The Effect of 0.01% Atropine Eye Drops Combined with Auricular Acupoint Stimulation on Myopia Progression and Choroidal Thickness: The Preliminary Results from a Randomized Controlled Trial

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Research

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Abstract

Background: Use of 0.01% atropine eye drops (0.01%A) is one of the most common treatments for myopia control for children in Asia. Auricular acupoint stimulation (AAS) was reported to enhance the effect of higher-concentration atropine (0.25%, 0.125%) on myopia control. This study was designed to compare the effect of 0.01%A combined with AAS and 0.01%A alone on myopia progression and choroidal thickness in children.

Methods: A total of 104 children were stratified by age and randomly assigned at 1:1 to receive 0.01%A or 0.01%A+AAS treatment for 6 months. Repeated measurements of cycloplegic spherical equivalent (SE) autorefraction, axial length (AL), and choroidal thickness were performed at baseline, 1 month, 3 months and 6 months.

Results: The adjusted mean SE change over the 6 months was −0.38 ± 0.04 D in the 0.01%A group (n = 50) and −0.25 ± 0.04 D in the 0.01%A+AAS group (n = 50), demonstrating a significant between-group difference ($P = 0.02$). There was no statistically significant difference in the change of AL or choroidal thickness between the two groups (both $P > 0.05$).

Conclusion: Compared with 0.01%A monotherapy, AAS as adjunctive treatment slowed myopic progression in Chinese children by a small, statistically amount during this 6-month observation. Future follow-up study is needed to verify its effects on axial elongation or choroidal thickness.

Trial registration: Trial registration: Chinese Clinical Trial Registry, ChiCTR1900021316. Registered 13 February 2019, http://www.chictr.org.cn/showproj.aspx?proj=35435

Background

The global prevalence of myopia is increasing rapidly in recent decades, predominantly in East Asia. Large-scale investigations conducted in China indicated that the prevalence of myopia is now 70–85% in students at the age of 17 to 18 [1–3], being much higher than that of 20–40% seen in many western countries [4–6]. High myopia predisposes the patients to a number of severe ocular complications, such as retinal detachment and macular degeneration, leading to loss of vision and blindness [7]. Therefore, myopia prevention and control has become an important issue to be solved urgently.

Acupoint stimulation is a traditional Chinese medicine therapy that can regulate whole body function to achieve a therapeutic effect. Chinese eye exercises have been performed by school children in China as an “acupoint pressing” intervention for the purpose of reducing ocular fatigue and preventing myopia for around 60 years, but the efficacy is still a matter of debate [8–10]. Acupuncture, as a promising acupoint stimulation measure, has long been used in ophthalmology diseases [11]. Shang et al. [12] showed that acupuncture reduced − 0.07 D myopia progression in a 5-week treatment, but the results were limited by small sample size and lack of a blank control. The efficacy of acupuncture depends on continuous treatment 2 to 3 times per week, which is less acceptable for children with heavy academic burden and

fear of needles. Auricular acupoint stimulation (AAS) may be a suitable choice for preventing myopia in children because of its simple and non-invasive operation. Two studies [13, 14] showed that auricular acupoint pressing could temporarily improve the unaided visual acuity and delay the progression of myopia compared with the blank control group, but the results were calculated based on non-cycloplegic refraction and the observation periods were short.

In recent years, administration of 0.01% atropine eye drops (0.01%A) has become one of the most common treatment modalities for myopia control for children in Asia [15]. Compared with blank control and placebo control, 0.01%A could slow myopia progression by roughly 0.25 D in one year [16, 17]. In contrast, the effect of 0.01%A on axial length (AL) elongation remains controversial [17, 18]. Therefore, a higher concentration atropine has been intended for children who showed poor response to 0.01% atropine. In LAMP2 study [19], the efficacy of 0.05% atropine on myopia control was twice that of 0.01% atropine. However, 0.05% atropine induced 2 D accommodative amplitude loss and 1.25 mm pupil dilation, not favorable in terms of long-term safety. Since AAS has been shown to enhance the effect of higher-concentration atropine (0.25% [20], 0.125% [21]) on myopia control, the question remains as whether AAS might also enhance the effect of 0.01%A without inducing significant side effects.

Being an integral part of the mechanisms underlying myopia onset and development, the choroid has been extensively explored in the last decade [22, 23]. Scleral hypoxia caused by choroidal thinning has been hypothesized to result in myopia progression [24]. Since AAS was reported to alter the blood flow velocity of ophthalmic artery [25], we speculate that AAS can promote the blood flow of choroid, which may in turn thicken the choroid and produce curative effect on myopia progression.

The purpose of the present study was to evaluate the effect of 0.01%A combined with AAS and 0.01%A alone on myopia progression and choroidal thickness in children.

Methods

Study design

This study was a prospective, randomized, assessor- and statistician-masked, controlled trial comparing the effect of 0.01%A+AAS and 0.01% A alone on myopia progression and choroidal thickness in Chinese children. The protocol and informed consent were approved by the Institutional Ethical Committee Review Board of Fudan University Eye & ENT Hospital and also was registered with Chinese Clinical Trial Registry (identifier: ChiCTR1900021316). All subjects were treated in accordance with the tenets of the Declaration of Helsinki.

Eligibility Criteria

The study recruitment was announced via an official account on social media. The guardians of the subjects were instructed to read the informed consent and those who responded positively were

scheduled for the screening visit. Inclusion criteria were: aged 7 to 12 years with myopic refraction between -6.00 D and +0.50 D, astigmatism of less than 1.50 D, anisometropia of less than 1.50 D, intraocular pressure between 10 to 21 mmHg. Excluded were those who had other ocular diseases (e.g., cataract, uveitis, amblyopia), auricular diseases or systemic diseases, allergy to atropine, previous use of atropine or any other myopia control treatment within 1 month. Informed consent was obtained from both subjects and their guardians.

Randomization and masking

In a permuted block design stratified by age (7 to 9, 10 to 12), each subject was randomly assigned with equal probability to receive 0.01%A treatment or 0.01%A+AAS treatment. The randomization sequence was generated by a third party using SPSS 24.0. The assessors and the statisticians were masked to the treatment allocation, while open to the acupuncturists. In the 0.01%A group, subjects and their guardians were told to remove the magnetic plasters before each assessment and not to discuss any issues related to auricular acupoint with the assessors.

Interventions

Subjects in 0.01%A group were treated with a single drop of 0.01% atropine eye drops (0.4ml:0.04mg, Shenyang Xingqi Pharmaceutical Co., Ltd., Shenyang, China) every night for 6 months. Subjects in 0.01%A+AAS group received 0.01% atropine treatment plus auricular acupoint stimulation for 6 months. Seven auricular acupoints on the ear, including Eye (LO5), Anterior Intertragic Notch (TG2l), Posterior Intertragicus (AT1l), Heart (CO15), Liver (CO12), Kidney (CO10), Shenmen (TF4) were selected as shown in Figure 1 according to traditional Chinese medicine theory based on review of the literature [14, 20, 21]. A magnetic bead plastered with 7mm tape (Hwato, Suzhou Medical Appliance Factory Co., Ltd., Suzhou, China) was used for acupoint stimulation. Pressing stimulation was administered 3 times per day (6:30-7:30, 15:30-16:30, 20:00-21:00) and 30 times for each acupoint. In order to avoid the decrease of acupoint sensitivity and skin allergy, only unilateral auricles were pressed every week, and bilateral auricles were carried out alternately. The acupoint plaster was changed weekly by licensed acupuncturists with more than 2 years' experience. At the same time, the teaching videos and maps describing AAS therapy were distributed to the guardians for learning, so that the magnetic beads fell from the acupoints by chance (e.g., bathing) could be pasted in time. Quality control was performed by the acupuncturists through checking the instant photos sent by the guardians.

Outcome measurements

After the screening visit (baseline), subjects were reassessed at 1, 3, and 6 months. At each visit, spherical equivalent (SE), axial length (AL) and choroidal thickness were measured.

Cycloplegic autorefraction was measured using an open-field autorefractor (WAM-5500, Grand Seiko Ltd, Japan) [26] 30 minutes after one drop of 0.5% Alcaine and two drops of 1% cyclopentolate HCL in 5-minute interval. This equipment allowed a sensitivity of 0.01 D, which could detect subtle diopter differences. The subjects were instructed to fixate on a Maltese cross at 5 m during measurements. If the subject's uncorrected visual acuity was < 6/12, a green spotlight was utilised to minimise eye movements. SE was calculated for autorefraction readings. Five SE outcomes were obtained and averaged.

AL was measured by a swept source optical coherence tomography based IOL-Master 700 (Carl Zeiss Meditec, Inc., Germany) [27]. Three readings of repeated measurements and difference no greater than 0.02 mm were taken and averaged.

Images of the choroid in the macular region were obtained using a spectral domain OCT (RS-3000, NIDEK, Japan). This OCT device uses a super luminescent diode of central wavelength 880 nm for OCT imaging, with an axial resolution of 7 μm and transverse resolution of 20 μm. A three-dimensional scanning procedure was performed with a 6 × 6 mm raster scan centered on the fovea, which was composed of 128 B-scans. Each image is the average of 10 scans and images with motion artifacts, blinking, or segmentation failure were not included in the data analysis.

Data analyses

The analysis for OCT imaging in terms of choroidal volume was processed in three steps: attenuation compensation, choroid segmentation, and en-face mapping. The attenuation compensation algorithm was proposed [28] to enhance the visibility of the sclera-choroid interface and to minimise the projection shadows of retinal vessels in previous publications [29, 30]. We then employed the U-shape convolutional network (U-Net) [31, 32] to automatically segment the choroid in OCT. The trained U-Net for the choroid segmentation here achieved an AUSDE of 2.65 pixels. We deployed it to segment the data used in this paper and manually checked the results afterwards. The segmentation results were used to calculate the subfoveal choroidal thickness (SChT) and average choroidal thickness (AChT) by manually localizing the fovea and averaging over the entire 6×6 mm^2 field of view, respectively. More methodological details are shown in Additional file 1.

Statistical analyses

Based on a previous study [20], the enhanced effect of AAS was assumed to be at least 0.17 D, with a common standard deviation of 0.28 D in each treatment group. The sample size was estimated to be 88 (44 per group) to achieve 80% power at a 0.05 significance level (two-sided). Considering a 10% non-adherence to treatment and a 5% loss to follow-up, a sample size of 104 subjects (52 per group) would be needed.

Full analysis set was performed based on the intention-to-treat principle. Since no statistically significant differences were found in baseline data between the two eyes, only data from right eyes were used for statistical analyses. Baseline characteristics between the two treatment groups was evaluated by unpaired t-tests for continuous data meeting normality assumptions and the chi-square test or the Fisher exact test for categorical data.

Generalised estimating equations (GEE), with one within-subject factor (time), one between-subject factor (treatment: 0.01%A or 0.01%A+AAS) and their interactions, was used to compare changes in all outcomes. Age, sex, baseline SE, number of myopic parents and outdoor time were included in the GEE model to determine the changes of SE and AL in the two study groups. Bonferroni adjustments were used for pairwise comparisons. Pearson correlation tests were used to evaluate the association between changes in SE and AL. We undertook ancillary analyses to confirm the treatment effects across potentially prognostic subgroups. These subgroups were sex, age, and baseline SE. The models also included the subgroup as a factor and the interaction between treatment and subgroup to test the significance of any difference in treatment effects across the subgroups. The significance level was set at $P < 0.05$.

Results

Figure 2 represents the flowchart of the study. A total of 116 subjects were assessed for eligibility, in which 104 subjects were recruited into the study, with 52 subjects allocated to the 0.01%A group and 52 subjects to the 0.01%A + AAS group. Eight subjects did not complete all the follow-up visits, with 4 in the 0.01%A group and 4 in the 0.01%A + AAS group. Among these eight subjects, four did not receive any assessment after baseline so their data were excluded from the analysis. Two subjects were unable to receive AAS treatment on schedule and the measurements at their final follow-up visits were carried forward. Two subjects commenced orthokeratology after three months' follow-up visit and their measurements at three months were carried forward. There was no statistically significant difference among groups in baseline characteristics of the two groups (all $P > 0.05$) (Table 1). The atropine use was 6.44 times per week (92%) in the 0.01%A group and 6.34 times per week (90.6%) in the 0.01%A + AAS group, respectively. The implementation of AAS was 2.56 times per day (85.3%). Both groups showed good compliance during treatment (> 85% expected use).

Table 1
Baseline characteristics of study subjects

	0.01%A (n = 50)	0.01%A + AAS (n = 50)	*P*
Age (years)	9.12 ± 1.39	8.96 ± 1.38	0.57
Gender, n (%)			
Male	22 (44%)	28 (56%)	0.23
Female	28 (56%)	22 (44%)	
Intraocular pressure (mmHg)	15.22 ± 2.51	15.39 ± 2.58	0.74
Spherical equivalent (D)	-2.25 ± 1.14	-2.14 ± 1.27	0.64
Axial length (mm)	24.48 ± 0.76	24.30 ± 0.86	0.25
Keratometry (D)	43.14 ± 1.53	43.46 ± 1.44	0.29
Anterior chamber depth (mm)	3.77 ± 0.21	3.78 ± 0.18	0.71
Lens thickness (mm)	3.34 ± 0.15	3.36 ± 0.14	0.48
Subfoveal choroidal thickness (μm)	233.45 ± 22.95	233.83 ± 28.68	0.95
Average choroidal thickness (μm)	219.94 ± 17.94	223.00 ± 19.59	0.46
Outdoor time (hours per week)[a]	8.14 ± 3.25	7.83 ± 3.46	0.48
Parental myopia, n (%)			
0	4 (8%)	2 (4%)	0.37
1	12 (24%)	18 (36%)	
2	34 (68%)	30 (60%)	
Values are means ± standard deviation unless stated otherwise.			
[a] Cumulative time outdoors from 7:00 to 17:00 except cloudy and rainy days.			

Change in SE

The tests of model effect indicated that treatment, time and age (all $P < 0.05$) had significant association with the magnitude of SE change.

The adjusted mean SE change over 6 months (Table 2, Fig. 3) was − 0.38 ± 0.04 D in the 0.01%A group (n = 50) and − 0.25 ± 0.04 D in the 0.01%A + AAS group (n = 50), being significantly different between groups

(mean differences 0.13 ± 0.06 D, *P* = 0.02). Controlling for covariates did not significantly change the result (P = 0.02).

Table 2
Change in ocular parameters at different timepoints

	0.01%A (n = 50)	0.01%A + AAS (n = 50)	P^a	P^b	P^c
Spherical equivalent (D)[d]					
Change at 1 m	-0.09 ± 0.03	-0.04 ± 0.03	0.23	< 0.001*	0.36
Change at 3 m	-0.20 ± 0.03	-0.13 ± 0.03	0.12		
Change at 6 m	-0.38 ± 0.04	-0.25 ± 0.04	0.02*		
Axial length (mm)[d]					
Change at 1 m	0.04 ± 0.04	0.03 ± 0.04	0.37	< 0.001*	0.46
Change at 3 m	0.12 ± 0.05	0.10 ± 0.05	0.28		
Change at 6 m	0.23 ± 0.05	0.20 ± 0.05	0.15		
Subfoveal choroidal thickness (μm)					
Change at 1 m	-0.74 ± 2.55	2.09 ± 2.71	0.36	0.033*	0.59
Change at 3 m	-3.15 ± 3.00	-1.57 ± 2.82	0.61		
Change at 6 m	-9.18 ± 2.76	-7.92 ± 2.92	0.55		
Average choroidal thickness (μm)					
Change at 1 m	-1.27 ± 1.60	0.04 ± 1.68	0.79		
Change at 3 m	-2.99 ± 1.87	-0.67 ± 1.69	0.21	0.039*	0.61
Change at 6 m	-4.75 ± 2.04	-3.00 ± 1.70	0.45		
Values are means ± standard error.					
[a] *P* value tests for group difference; [b] *P* value tests for time; [c] *P* value tests for the interaction between treatment and time. [d] Adjusted for age, sex, baseline spherical equivalent, number of myopic parents and outdoor time.					
*Significant at 0.05.					

The 6-month change in SE stratified by baseline characteristics is shown in Table 3. As indicated by the interaction terms from the model analyses, the enhancement effect of AAS was not related to age (*P* = 0.30), sex (*P* = 0.70), or baseline SE (*P* = 0.07). However, compared with subjects at the age of 10 to 12, those who were at the age of 7 to 9 had a significantly less SE change in the 0.01%A + AAS group than in

the 0.01%A group (mean differences 0.18 ± 0.06 D, $P = 0.01$). Compared with subjects with baseline SE ≥ -2.25 D, those who had baseline SE < -2.25 D had a significantly less SE change in the 0.01%A + AAS group than in the 0.01%A group (mean differences 0.25 ± 0.07 D, $P < 0.001$).

Table 3
Adjusted 6-month change in myopia progression stratified by baseline characteristics

Baseline characteristics	0.01%A	0.01%A + AAS	P^b	P^c
	Changes in spherical equivalent (D)[a]			
Age (years)				
7 ~ 9	-0.47 ± 0.05 (31)	-0.29 ± 0.05 (35)	0.01*	0.30
10 ~ 12	-0.23 ± 0.05 (19)	-0.17 ± 0.07 (15)	0.8	
Gender				
Male	-0.42 ± 0.07 (22)	-0.27 ± 0.05 (28)	0.08	0.70
Female	-0.33 ± 0.05 (28)	-0.23 ± 0.07 (22)	0.22	
Spherical equivalent (D)				
≥-2.25	-0.38 ± 0.05 (27)	-0.31 ± 0.05 (32)	0.64	0.07
<-2.25	-0.38 ± 0.06 (23)	-0.13 ± 0.07 (18)	< 0.001*	
	Changes in axial length (mm)[a]			
Age (years)				
7 ~ 9	0.27 ± 0.03 (31)	0.22 ± 0.02 (35)	0.14	0.61
10 ~ 12	0.19 ± 0.02 (19)	0.17 ± 0.04 (15)	0.57	
Gender				
Male	0.26 ± 0.03 (22)	0.21 ± 0.03 (28)	0.07	0.13
Female	0.21 ± 0.02 (28)	0.19 ± 0.03 (22)	0.63	
Spherical equivalent (D)				
≥-2.25	0.23 ± 0.02 (27)	0.23 ± 0.02 (32)	0.57	0.09
<-2.25	0.24 ± 0.03 (23)	0.16 ± 0.03 (18)	0.03*	

Values are means ± standard error.

[a] Adjusted for age, sex, baseline spherical equivalent, number of myopic parents and outdoor time unless stratified by that factor. [b] *P* value tests for group difference. [c] *P* value tests for the interaction between treatment and baseline characteristics.

*Significant at 0.05.

Change in AL

The tests of model effect indicated that time and age (both $P < 0.05$) had significant association with the magnitude of AL increase.

The adjusted increase of AL over 6 months (Table 2, Figure 3) was 0.23 ± 0.05 mm in the 0.01%A group (n = 50) and 0.20 ± 0.05 mm in the 0.01%A+AAS group (n = 50), with no significant differences between groups ($P = 0.15$). Controlling for covariates did not significantly change the result. ($P = 0.19$).

AL elongation over 6 months stratified by baseline characteristics is shown in Table 3. Interaction analyses revealed that the effect of AAS treatment was not correlated to age ($P = 0.61$), sex ($P = 0.13$), or baseline SE ($P = 0.09$). However, significant differences between groups were observed in subjects with baseline SE < -2.25 D (mean differences -0.08 ± 0.03 mm, $P = 0.02$).

Overall, the Pearson correlation coefficient between the change in AL and the change in SE was 0.78 for the 0.01%A group and 0.81 for the 0.01%A+AAS group (both $P < 0.001$).

Change in Choroidal thickness

The tests of model effect indicated that only time had a significant association with SChT ($P = 0.033$) and AChT ($P = 0.039$). A relatively small amount of SChT thinning at 6 months was found in both the 0.01%A group (-9.18 ± 2.76 μm, $P < 0.001$) and the 0.01%A+AAS group (-7.92 ± 2.92 μm, $P < 0.001$) while AChT thinning at 6 months was only found in the 0.01%A group (-4.75 ± 2.04 μm, $P = 0.033$) after Bonferroni correction. However, no differences in SChT ($P = 0.55$) or AChT (P = 0.45) were observed between groups.

Discussion

In this randomized clinical trial, we found a statistically significant 6-month enhancement effect of adjunctive AAS ($P = 0.02$), with an adjusted mean difference of 0.13 D in SE change between the 0.01%A + AAS and the 0.01%A group. This difference was clinically negligible, yet statistically significant. In concordance with our finding, Liang et al. [20] found that the adjunctive AAS treatment with 0.25% atropine eye drops slowed myopia progression by 0.17 D and Chen et al. [21] found that the adjunctive AAS treatment with 0.125% atropine eye drops slowed myopia progression by 0.25 D over 12-month follow-up. Surprisingly, there was no significant difference in AL change between the two groups in the current study. Since the change in SE was highly correlated with changes in AL and the correlation coefficients were almost similar between the two groups (0.78 in the 0.01%A group and 0.81 in the 0.01%A + AAS group), it remains unclear why there is a mismatch between the two parameters. Our sample size may be too small and the observational span too short to detect the AL difference between the two groups. We speculate that the enhancement effect may continue to accumulate over next 6-month follow-up.

Ancillary analyses showed that children with higher myopia or lower age might benefit more from AAS as an adjunctive treatment. This phenomenon may be explained by the theory of “acupoint sensitization” [33] that the status of acupoints can switch from a “silent” to “active” state during pathological processes and stimulating sensitized acupoints can exert a better effect. According to Donovan’s study [34], myopia progression declines from − 1.12 D/y at 7 years old to -0.50 D/y at 12 years old among Asian children. Additionally, more myopic baseline refractive error was related to higher risk of myopia [35] and high myopia [36] onset. Therefore, the myopia-related acupoints of children in these two subgroups were likely to be more active, which might be the reason why they benefited more from the combined AAS treatment.

Previous studies have suggested that choroid may play a bridging role in the signal cascades of myopia development. A bi-directional change of choroidal thickness in response to different retinal defocus signals was found in both human eyes and animal models [37–39]. Thinning of the choroid may lead to scleral hypoxia, which promote scleral extracellular matrix remodeling and myopia ensues consequently [24]. In the current study, we did not find a significant effect of AAS treatment on SChT or AChT at 1 month, 3 months, or 6 months. This suggests that the choroidal thickness change is unlikely to act as a primary mechanism to promote the enhancement effect of AAS in slowing myopia progression. Further studies are needed to explore the underlying mechanism.

High concentration atropine (1%, 0.5%) eye drops have been shown to increase choroidal thickness and eliminate the effect of hyperopic defocus on choroidal thinning in human eyes [40, 41]. In contrast, the impact of low concentration atropine (0.01%) on choroidal thickness remains controversial. Studies with positive results revealed a much less choroidal thickening, e.g., 6 μm after 1 hour [42] and 5 μm after 1 month use of 0.01%A [43]. Since some children who experience fast AL growth will exhibit a thinning of the choroid [23], it is not surprising that we found a slightly thinner choroid after 0.01%A use for 6 months. The inconsistency between the previous studies and the current one could also be explained by the different OCT methodologies applied. We adopted an automatic segmentation method through machine deep learning as opposed to manual differentiation of the choroidal boundary as used by most of the other studies, which inevitably incurs human artifacts. The long-term impact of 0.01%A or combined with AAS on choroidal thickness warrants further investigation.

Our study has some limitations. First, we didn’t use sham acupoint plaster with no bead as adjunctive intervention in the 0.01%A group for placebo control. Since AAS is widely used in China and soreness caused by pressing is well recognized by many people, it is difficult to implement a sham intervention by using a bead-free acupoint plaster as a placebo. Second, this study has no blank control group without any pharmaceutical intervention. Therefore, the question as to whether the two treatment modalities applied in this study has any effect on myopia progression remains unanswered. Third, this study was limited by its small sample size, and studies with longer observational span and larger sample size are needed to illustrate whether the enhancement effect of AAS is sustainable.

Conclusion

To conclude, adjunctive AAS compared with 0.01%A monotherapy slows myopic progression in Chinese children, but has no effect on axial elongation and choroidal thickness within 6 months of treatment. Children with higher myopia and lower age might benefit more from AAS as an adjunctive treatment.

Abbreviations

AAS: Auricular acupoint stimulation; AChT: Average choroidal thickness; AL: Axial length; LAMP: Low-concentration atropine for myopia progression; SChT: Subfoveal choroidal thickness; SE: Spherical equivalent; 0.01%A: 0.01% atropine eye drops.

Declarations

Ethics approval and consent to participate

The protocol and informed consent were approved by the Institutional Ethical Committee Review Board of Fudan University Eye & ENT Hospital (No. 2019013). Written informed consent was obtained from all eligible participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XM and XZ had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XM and ZS contributed to the conception of this trial. XK and YZ contributed to the design of this trial and to manuscript writing. ZC and XZ revised the manuscript. ZC, LZ, GY, YY and DZ participated in clinical evaluation and enrollment. RH, XD, XG took part in data collection and analysis. All authors read and approved the final manuscript.

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References

1. You QS, Wu LJ, Duan JL, Luo YX, Liu LJ, Li X, et al. Prevalence of myopia in school children in greater Beijing: the Beijing Childhood Eye Study. Acta Ophthalmol. 2014;92:e398-406.
2. Guo K, Yang DY, Wang Y, Yang XR, Jing XX, Guo YY, et al. Prevalence of myopia in schoolchildren in Ejina: the Gobi Desert Children Eye Study. Invest Ophthalmol Vis Sci. 2015;56:1769-1774.
3. Wu JF, Bi HS, Wang SM, Hu YY, Wu H, Sun W, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. PLoS One. 2013;8:e82763.
4. Cumberland PM, Bao Y, Hysi PG, Foster PJ, Hammond CJ, Rahi JS, et al. Frequency and Distribution of Refractive Error in Adult Life: Methodology and Findings of the UK Biobank Study. PLoS One. 2015;10:e0139780.
5. Williams KM, Verhoeven VJ, Cumberland P, Bertelsen G, Wolfram C, Buitendijk GH, et al. Prevalence of refractive error in Europe: the European Eye Epidemiology (E^3) Consortium. Eur J Epidemiol. 2015;30:305-315.
6. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. Ophthalmic Physiol Opt. 2012;32:3-16.
7. Saw S-M, Gazzard G, Shih-Yen EC, Chua W-H. Myopia and associated pathological complications. Ophthalmic Physiol Opt. 2005;25:381-391.
8. Kang MT, Li S-M, Peng X, Li L, Ran A, Meng B, et al. Chinese Eye Exercises and Myopia Development in School Age Children: A Nested Case-control Study. Sci Rep.6:28531.

9. Wang H, Qian Y, Congdon N, Boswell M, Rozelle S, Ma X. Effect of Chinese eye exercises on change in visual acuity and eyeglasses wear among school-aged children in rural China: a propensity-score-matched cohort study. BMC Complement Med Ther. 2020;20:82.
10. Lin Z, Vasudevan B, Fang SJ, Jhanji V, Mao GY, Han W, et al. Eye exercises of acupoints: their impact on myopia and visual symptoms in Chinese rural children. BMC Complement Altern Med. 2016;16:349.
11. Wong S, Ching R. The use of acupuncture in ophthalmology. Am J Chin Med. 1980;8:104-153.
12. Shang X, Chen L, Litscher G, Sun Y, Pan C, Liu CZ, et al. Acupuncture and Lifestyle Myopia in Primary School Children-Results from a Transcontinental Pilot Study Performed in Comparison to Moxibustion. Medicines (Basel). 2018;5.
13. Li Y, Zhang O, Liang W, Li C. Effect of auricular pressing treatment on myopia in children. J Tradit Chin Med. 2015;35:281-284.
14. Chen CH, Chen HH, Yeh ML, Tsay SL. Effects of ear acupressure in improving visual health in children. Am J Chin Med. 2010;38:431-439.
15. World Health Organization, Brien Holden Vision Institute. The impact of myopia and high myopia: report of the Joint World Health Organization–Brien Holden Vision Institute Global Scientific Meeting on Myopia, University of New South Wales, Sydney, Australia, 16–18 March 2015. Geneva: World Health Organization. 2016:15. https://www.who.int/blindness/causes/MyopiaReportforWeb.pdf?ua=1&ua=1
16. Fu A, Stapleton F, Wei L, Wang W, Zhao B, Watt K, et al. Effect of low-dose atropine on myopia progression, pupil diameter and accommodative amplitude: low-dose atropine and myopia progression. Br J Ophthalmol. 2020;0:1-7.
17. Yam JC, Jiang Y, Tang SM, Law AKP, Chan JJ, Wong E, et al. Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control. Ophthalmology. 2019;126:113-124.
18. Chia A, Lu QS, Tan D. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2: Myopia Control with Atropine 0.01% Eyedrops. Ophthalmology. 2016;123:391-399.
19. Yam JC, Li FF, Zhang X, Tang SM, Yip BHK, Kam KW, et al. Two-Year Clinical Trial of the Low-Concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report. Ophthalmology. 2020;127:910-919.
20. Liang CK, Ho TY, Li TC, Hsu WM, Li TM, Lee YC, et al. A combined therapy using stimulating auricular acupoints enhances lower-level atropine eyedrops when used for myopia control in school-aged children evaluated by a pilot randomized controlled clinical trial. Complement Ther Med. 2008;16:305-310.
21. Cheng HC, Hsieh YT. The effect of low-concentration atropine combined with auricular acupoint stimulation in myopia control. Complement Ther Med. 2014;22:449-455.
22. Liu B, Wang Y, Li T, Lin Y, Ma W, Chen X, et al. Correlation of subfoveal choroidal thickness with axial length, refractive error, and age in adult highly myopic eyes. BMC Ophthalmol. 2018;18:127.

23. Read SA, Alonso-Caneiro D, Vincent SJ, Collins MJ. Longitudinal changes in choroidal thickness and eye growth in childhood. Invest Ophthalmol Vis Sci. 2015;56:3103-3112.
24. Wu H, Chen W, Zhao F, Zhou Q, Reinach PS, Deng L, et al. Scleral hypoxia is a target for myopia control. Proc Natl Acad Sci U S A. 2018;115:E7091-E7100.
25. Litscher G. Computer-based quantification of traditional chinese-, ear- and Korean hand acupuncture: needle-induced changes of regional cerebral blood flow velocity. Neurol Res. 2002;24:377-380.
26. Sheppard AL, Davies LN. Clinical evaluation of the Grand Seiko Auto Ref/Keratometer WAM-5500. Ophthalmic Physiol Opt. 2010;30:143-151.
27. Akman A, Asena L, Güngör SGJBJoO. Evaluation and comparison of the new swept source OCT-based IOLMaster 700 with the IOLMaster 500. Br J Ophthalmol. 2015;100:1201-1205.
28. Girard MJA, Strouthidis NG, Ethier CR, Mari JM. Shadow Removal and Contrast Enhancement in Optical Coherence Tomography Images of the Human Optic Nerve Head. Invest Ophthalmol Vis Sci. 2011;52:7738-7748.
29. Vupparaboina KK, Dansingani KK, Goud A, Rasheed MA, Jawed F, Jana S, et al. Quantitative shadow compensated optical coherence tomography of choroidal vasculature. Sci Rep. 2018;8:6461.
30. Zhou H, Chu Z, Zhang Q, Dai Y, Gregori G, Rosenfeld PJ, et al. Attenuation correction assisted automatic segmentation for assessing choroidal thickness and vasculature with swept-source OCT. Biomed Opt Express. 2018;9:6067-6080.
31. Ronneberger O FP, Brox T. U-net: Convolutional networks for biomedical image segmentation. International Conference on Medical image computing and computer-assisted intervention. 2015:234-241. https://doi.org/10.1007/978-3-319-24574-4_28
32. Ibtehaz N, Rahman MS. MultiResUNet : Rethinking the U-Net architecture for multimodal biomedical image segmentation. Neural Netw. 2020;121:74-87.
33. Tan H, Tumilty S, Chapple C, Liu L, McDonough S, Yin H, et al. Understanding Acupoint Sensitization: A Narrative Review on Phenomena, Potential Mechanism, and Clinical Application. Evid Based Complement Alternat Med. 2019;2019:6064358.
34. Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith EL, Holden BA. Myopia progression rates in urban children wearing single-vision spectacles. Optom Vis Sci. 2012;89:27-32.
35. Zadnik K, Sinnott LT, Cotter SA, Jones-Jordan LA, Kleinstein RN, Manny RE, et al. Prediction of Juvenile-Onset Myopia. JAMA Ophthalmol. 2015;133:683-689.
36. Chen Y, Han X, Guo X, Li Y, Lee J, He M. Contribution of Genome-Wide Significant Single Nucleotide Polymorphisms in Myopia Prediction: Findings from a 10-year Cohort of Chinese Twin Children. Ophthalmology. 2019;126:1607-1614.
37. Chakraborty R, Read SA, Collins MJ. Hyperopic defocus and diurnal changes in human choroid and axial length. Optom Vis Sci. 2013;90:1187-1198.
38. Chakraborty R, Read SA, Collins MJ. Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. Exp Eye Res. 2012;103:47-54.

39. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. Vision Res. 1995;35:1175-1194.
40. Zhang Z, Zhou Y, Xie Z, Chen T, Gu Y, Lu S, et al. The effect of topical atropine on the choroidal thickness of healthy children. Sci Rep. 2016;6:34936.
41. Chiang ST, Phillips JR. Effect of Atropine Eye Drops on Choroidal Thinning Induced by Hyperopic Retinal Defocus. J Ophthalmol. 2018;2018:8528315.
42. Sander BP, Collins MJ, Read SA. Short-Term Effect of Low-Dose Atropine and Hyperopic Defocus on Choroidal Thickness and Axial Length in Young Myopic Adults. J Ophthalmol. 2019;2019:4782536.
43. Zhao W, Li Z, Hu Y, Jiang J, Long W, Cui D, et al. Short-term effects of atropine combined with orthokeratology (ACO) on choroidal thickness. Cont Lens Anterior Eye. 2020.
44. The World Federation of Acupuncture-Moxibustion Societies, Auricular acupuncture point. World J Acupunct Moxibustion. 2013;23:12-21.

Figures

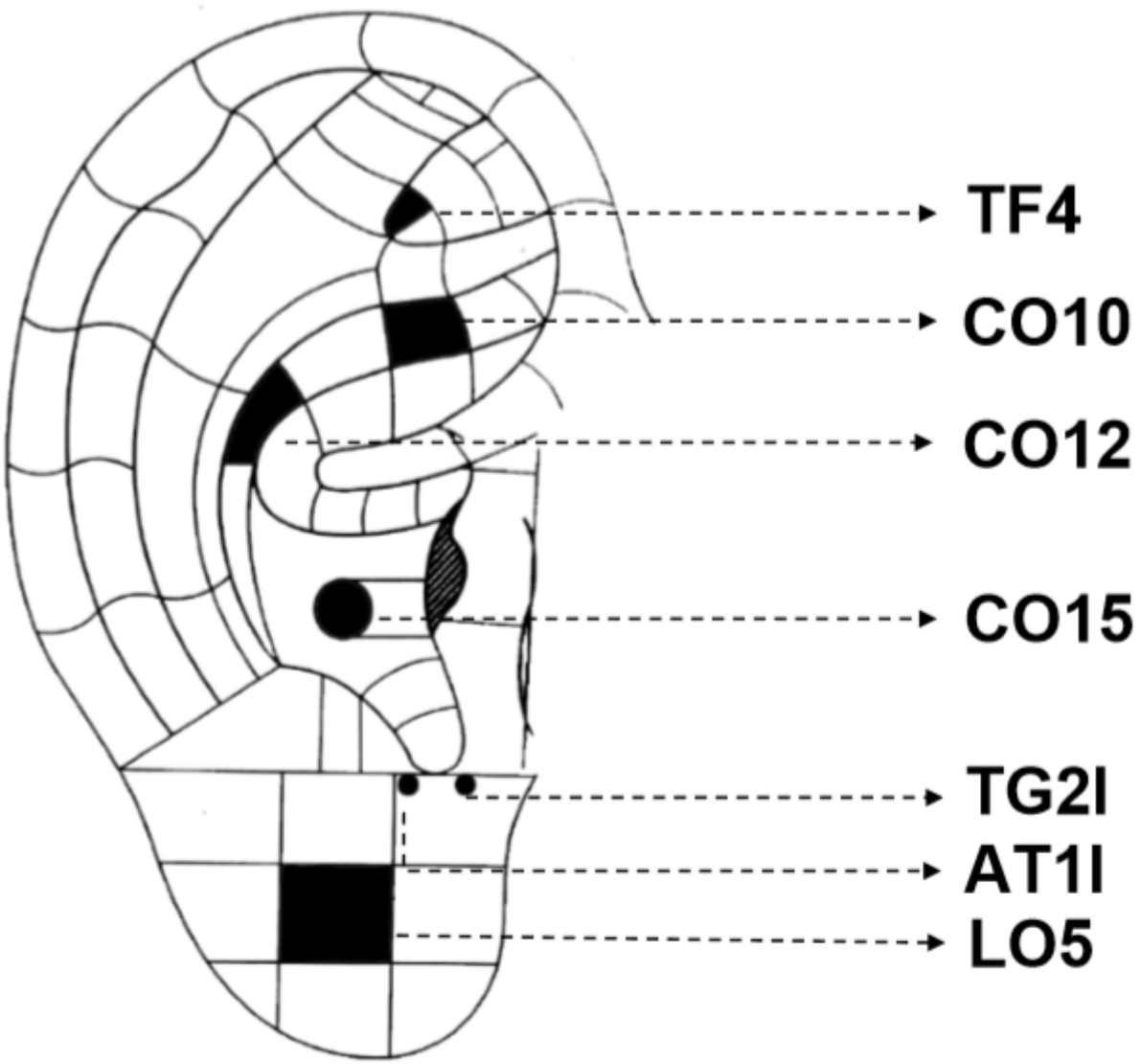

Figure 1

Selected auricular points for preventing myopia. This picture was modified according to the auricular map issued by World Federation of Acupuncture-Moxibustion Societies [44].

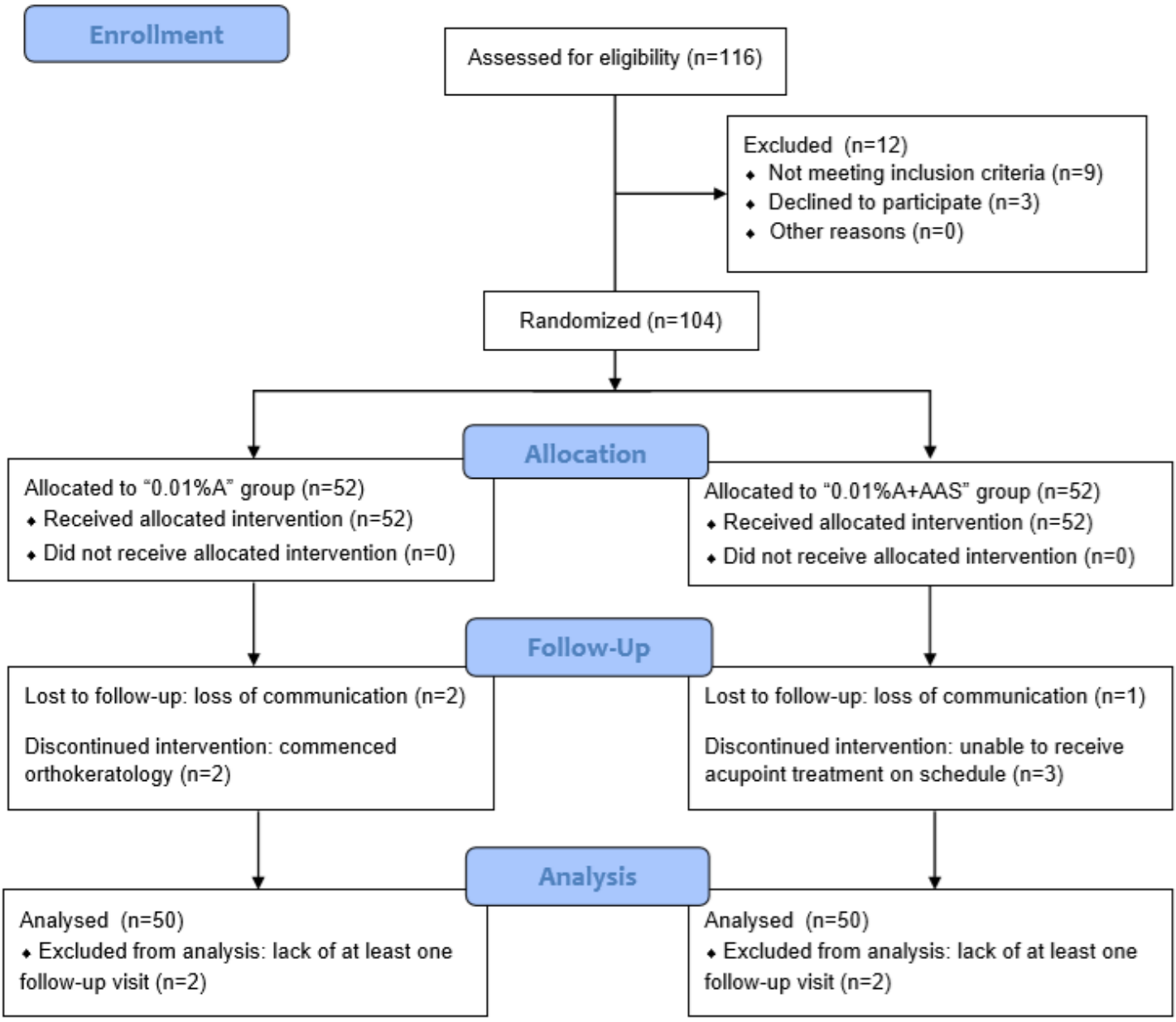

Figure 2

Schematic diagram showing the study flow

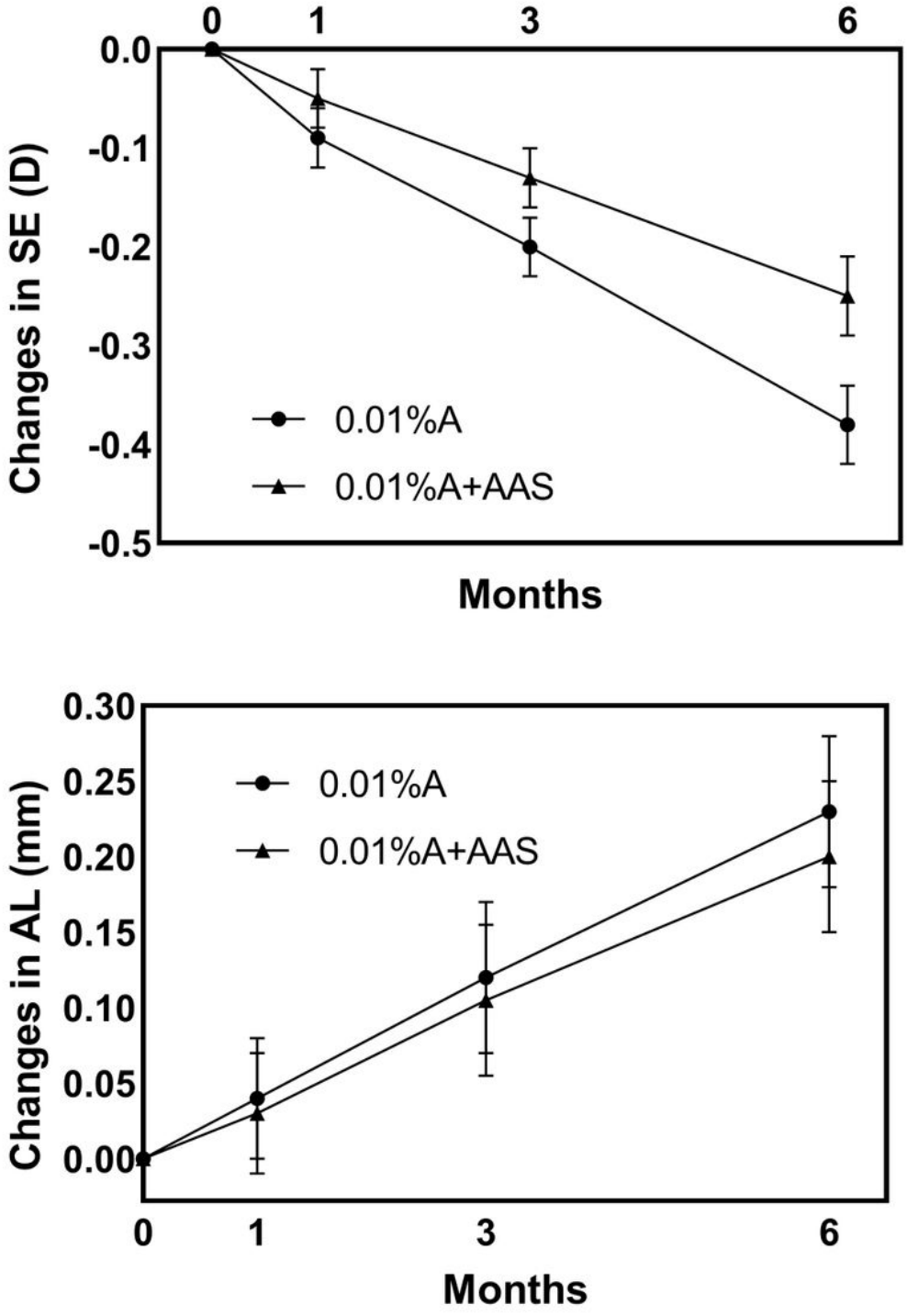

Figure 3

Adjusted mean change of myopia progression from baseline to 6 months. SE, spherical equivalent; AL, axial length.

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