Atropine for Myopia Progression Control Study

Shanghai Eye Disease Prevention and Control

Center/Shanghai Eye Hospital, Shanghai General

Hospital

May 2019

1. Introduction:

1.1 Myopia is a major public health problem around the world

At present, myopia has become a major public health problem. World Health Organization (WHO) statistics show that there are about 75 million visual impairment patients in China, 2010, and uncorrected myopia is the first cause (42%). Over the past 50-60 years, the prevalence of myopia in East Asia such as China has risen rapidly, and the incidence of myopia shows a progressive trend after the onset of early age. In cities, the prevalence of myopia among middle school students is over 70%, and among high school graduates, 80-90% are myopia, of which 10-20% are high myopia. According to the degree of myopia, myopia above - 6D is defined as high myopia. The harm of high myopia mainly lies in its complications, some blinding eye diseases, such as macular degeneration and retinal detachment, are caused by corresponding changes of other tissues in the eye, and the quality of life of patients with high myopia is seriously affected. Morgan et al. pointed out in the comments of myopia experts published in Lancet in 2012 that the risk of complications such as posterior scleral staphyloma, choroidal neovascularization, retinal splitting and choroidal atrophy, which may cause blindness, has increased dramatically in a large number of new-onset high myopic people in Asia in the past 100 years. WHO has considered the prevention and treatment of myopia as part of the global blindness prevention plan, especially in East Asia. Recent epidemiological studies on ophthalmopathy show that with the improvement of the national ophthalmological service level, the rate of cataract surgery has increased rapidly, and the proportion of cataract-curable blindness in the population has continued to decline, while high myopia-Related retinopathy has gradually become the first irreversible blinding eye disease in China.

1.2 The overview of high myopia

From the occurrence of high myopia to pathological myopia and the final occurrence of blindness and visual impairment is a long-term process. First, myopia occurs in early childhood (the age of initial myopia is often before school age). The growth rate of myopia is significantly higher than that of most people. It often exceeds - 6D at the age of 15 (graduation from junior middle school). Secondly, unlike myopia in general children, myopia degree and axis length continue to progress in adulthood. With the extension of eye axis, posterior choroid and sclera continue to develop and become thinner. When pathological changes such as chorioretinal atrophy and choroidal neovascularization occur, they are generally over 50 years old. In order to avoid blindness and visual impairment caused by complications of high myopia, it is necessary to start myopia screening and intervention from childhood and adolescence.

1.3 Studies about atropine for controlling myopia progression

In order to reduce the incidence of high myopia, many myopia control interventions have been carried out in children and adolescents at home and abroad. Among them, atropine, an M-receptor antagonist, has been shown to be effective in myopia control in many experimental and clinical trials in recent years. In ATOM2 study in Singapore, a randomized controlled clinical trial was conducted. Two years after the use of 1% atropine eye drops, children's myopia decreased by 0.92D and eye axis increased by 0.4mm compared with the control group. After 2 years of treatment with 0.5%, 0.1% and 0.01% respectively, the myopia of children increased by 0.30D, 0.38D and 0.49D, respectively, which were

significantly lower than that of the control group (1.20D). Although 1% atropine eye drops had myopic rebound effect after discontinuation, the rebound effect disappeared when the concentration of atropine was reduced to 0.1% and 0.01%.

In the LAMP study in Hong Kong, after one year of treatment with 0.05%, 0.025% and 0.01% respectively, the myopia of children increased by 0.27D, 0.46D and 0.59D, which were significantly lower than that of the control group (0.81D), and the ocular axis increased by 0.20mm, 0.29mm and 0.36mm, respectively, which were lower than that of the control group (0.41mm). Similar studies at home and abroad have also confirmed that the use of low-concentration atropine has a good effect on myopia control. At present, in Taiwan, Hong Kong, Singapore and other Chinese areas, children with high myopia risk and rapid growth of myopia have been more commonly treated with low-concentration atropine eye drops for intervention.

The mechanism of atropine controlling myopia has not been fully elucidated. Early studies suggested that atropine could control myopia by regulating mechanism. However, McBrien found that atropine could still control the development of myopia after cutting off the regulating pathway through animal experiments. Therefore, the mainstream view is that atropine controls myopia by non-regulating mechanism. It may be through the antagonism of M receptor signaling pathway on the retina or scleral surface to slow down the development of myopia, but the specific mechanism has not yet been fully elucidated. Atropine eye drops belong to mydriasis and ciliary paralysis drugs. Long-term use of atropine eye drops can lead to symptoms such as dilatation of pupils, photophobia and blurring of close-range objects. These symptoms are closely related to drug concentration and frequency of use.

1.4 The objectives of our study

From previous studies, investigators can find that 1% atropine has good effect in early myopia control, but its side effects are great, long-term use compliance is poor, and there is a rebound effect; 0.01% atropine has poor effect in early myopia control, and the effect of follow-up for one year is not as good as 0.05%, but the effect of follow-up for two years is equal to 1%, that is, long-term use effect is good, and there are few side effects. Considering that only 1% or 0.01% atropine eyedrops (gels) are available in atropine eyedrops approved by the drug administration, investigators consider whether 1% atropine can be used for six months, and 0.01% atropine for one and a half years to achieve better early myopia control, late consolidation efficacy and side effects. In addition, the current clinical studies mainly focus on diopter and ocular axis. This project will explore the changes of lens and fundus after atropine treatment, whether there are indicators that reflect the effect of atropine control earlier and more accurately than diopter and ocular axis, and explore the target of atropine for myopia control.

2. Research Objectives

To explore a better way to control myopia progression and eliminate adverse effects at the same time;

To provide reliably evidence for clinical guideline of atropine use in children;

To investigate the mechanism of atropine on eyes.

3.Trail Design

a randomized controlled, prospective cohort study, no mask.

3.1 Eligibility

3.1.1 Case Selection Criteria

- 7-12 years old (grade 1 to grade 6 of primary school);
- Spherical Equivalent ranged from - 0.5D to - 6.0D, astigmatism < 0.75D, binocular diopter gap < 1.0D;
- No ophthalmopathy except ametropia was found.

3.1.2 Exclusion criteria for cases

- has amblyopia, strabismus and other eye diseases.
- Serious allergy to atropine eye drops;
- Atropine eye drops have been used to control myopia.
- Other therapeutic eye drops are being used or have not been discontinued for more than a month.
- There is a contraindication of mydriasis.
- Patients with severe heart, lung, liver, gallbladder and kidney diseases;
- Patients who had to take other drugs because of other diseases affected the results of this test;
- Those who have participated in other clinical trials in the past three months;
- Researchers believe that there are other unsuitable participants.

3.2 Groups and Sample size

Myopic children aged from 7-12 years old are randomly allocated into two groups: combined use of atropine sulfate 1% ophthalmic ointment and atropine sulfate 0.01% eye drop (experimental group) and atropine sulfate 0.01% eye drop (control group). Each group includes 111 participants.

3.3 Medications and usage:

3.3.1 control group: atropine sulfate 0.01% eye drop, once a day, once a drop, for two years;

3.3.2 Combined application group: atropine sulfate 1% ophthalmic ointment, once a day for the first week, once a drop for both eyes; and then once a week, once a drop for both eyes for half a year. Half a year later, atropine sulfate 0.01% eye drop is used once a day, one drop each time, with both eyes for one and a half years. Usage: Drop it into conjunctival sac, about the size of a rice grain, press the nasal root with thumb and index finger for 2 minutes after dripping, and use it before going to bed. Patients once a week are advised to use it before going to bed on Friday night.

3.4 Examination

3.4.1. Examination process: The brief process is as follows: Identity information registration > height, weight > naked eye vision & wearing vision > intraocular pressure > accommodation, near vison acuity > mesopic pupil size > slit lamp anterior segment

examination > cycloplegia > Autorefraction and subjective refraction > IOL-Master, Pentacam, Swept-source optical coherence tomography（SS-OCT，Topcon), wide-angle optical coherence tomography angiography(OCTA,Zeiss-9000)> fill out the questionnaire.

3.4.2 Ophthalmology inspection project operation rules

3.4.2.1 Vision test:The eyesight examination used the ETDRS visual acuity chart (LCD backlit lamp, WH0701), the test distance was 4 meters, and the visual target at 20/20 was the same height as the eye of the examinee. The recognition time of each visual target is 2~3s; the eye of the subject is required to be opened normally for examination, and the blinking, hoeing, neck stretching and peeking are strictly prevented. Vision is converted to a decimal count record. Visual acuity examination includes two parts: uncorrected visual acuity (UCVA) and corrected visual acuity (CVA). Children who are not wearing glasses are only examined by UCVA, and children who wear glasses are required to check CVA after completing the UCVA test.

3.4.2.2 Intraocular pressure measurement Intraocular pressure was measured using a non-contact tonometer (NT-4000, Nidek, USA). Each eye was repeatedly measured 3 times and averaged, and the difference between each two was less than 5 mmHg. Those with an intraocular pressure higher than 24 mmHg should be recorded and added for visual field examination.

3.4.2.3 Accommodation, near visual acuity: Accommodation is measured using a Royal Air Force (RAF) near point rule (Harlow, Essex, UK) with best-corrected distance spectacle correction. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced logMAR reading chart placed at 40 cm under well-lit conditions

3.4.2.4 Mesopic pupil size: measured by automated computer refractometer (KR-8900, Topcon, Japan) after staying in a dark room for 5 minutes at least. At least 5 pupil size readings were recorded and averaged.

3.4.2.5 Ophthalmologist examination Ophthalmologist examinations included anterior segment slit lamp examination (66 Vision. Tech, Suzhou, China) and ophthalmoscopy examination(66 Vision. Tech, Suzhou, China). To exclude those children with cycloplegia contradictions.

3.4.2.6 Cycloplegia The cycloplegia procedure is as follows: 1 drop of 0.5% proparacaine (Alcaine, Alcon) is added to the conjunctival sac of each eye, and 1 drop of 1% cyclopentolate is added to each eye after 15 seconds. (Cyclogyl, Alcon), 5 minutes apart. After each drip, ask the participant to press the inner canthus for a few seconds gently and try to take the head back posture. The last drop of cyclopentolate was instilled into the conjunctival sac for 30 minutes to check for light reflection. If the light reflection disappeared and the pupil diameter was greater than 6 mm, cycloplegia was considered complete. If the light reflection still exists, add a third drop of cyclopentolate, and re-

examine the light reflection and pupil diameter after 20 minutes. If there was still light reflection, the inspector needs to record this. During cycloplegia, if the participant has symptoms of ocular discomfort, the ophthalmologist should carefully examine it and give an appropriate treatment.

3.4.2.7 Axis measurement: The axial measurement was performed using an IOL Master (version 5.02, Carl Zeiss Meditec, Germany). Simulated eye calibration was needed before measurement. Each eye was measured repeatedly for 3 times, and the difference was less than 0.02 mm each time. For those who still have large fluctuations in multiple measurements, the examiner needs to record it.

3.4.2.8 Measurement of refractive state and corneal radius of curvature (CR) The refractive status and CR measurements were performed using an automated computer refractometer (KR-8900, Topcon, Japan), which was performed after ciliary muscle paralysis. Simulated eye calibration needed before measurement. Each eye was repeatedly measured three times to average, and if any two results differ by more than 0.5 D, the measurement needed to be repeated. If there were still significant differences in the results of multiple measurements, the examiner needed to record it.

3.4.2.9 Subjective optometry Children who do not wear glasses have a UCVA of less than 0.8 (less than 0.63 for children 6 years of age and younger) or children with glasses have a CVA of less than 0.8 (children under 6 years of age and below 0.63) need to finish a subjective optometry after cycloplegia in order to measure the best corrected visual acuity (BCVA). If the BCVA is less than 0.8 (less than 0.63 for children aged 6 and under), or the degree of compliance during the examination is poor, the examiner should record it. If the BCVA is less than 0.8 (children under 6 years of age and below is less than 0.63), further examination by an ophthalmologist is required to determine whether the inclusion conditions are still met.

3.4.2.10 Pentacam (OCULUS Optikgeratic Gmbh, Germany) was examined after cycloplegia. Measurements include corneal diameter and curvature, anterior chamber depth and volume, anterior chamber angle, pupil diameter, crystal thickness, etc. Shooting requirements: Image quality display "OK", crystal thickness value is available. This item is optional for children under 6 years old.

3.4.2.11 SS-OCT （Topcon） SS-OCT (DRI OCT Triton, Topcon, Tokyo, Japan) was examined after cycloplegia. OCT location: Macular + optic disc area. Shooting mode: 12*9 mm 3D scan mode (4 overlap) / Line scan (64 overlap) + 9 mm radial scan mode (16 overlap, follow up mode) + optic disc area 9 Mm radial scan mode (16 overlap, follow up mode) + macular area 7*7 mm 3D scan mode (4 overlap) + optic disc area 6*6 mm 3D scan mode (4 overlap). Shooting requirements: input spherical error, cylinder, axis length, corneal curvature radius correction magnification before shooting; image signal of strength 3D scan mode is not less than 50, radial scan mode is not lower than 60, peripheral image avoids mirror flip as much as possible. When shooting the disc area, we need to manually adjust the shooting center to the center of the disc. If the image quality is affected by blinking or eye movement during shooting, participants need to re-shoot. If

participants still can't meet the requirements, participants need to record it. SS-OCT comes with a fundus color photograph. The shooting position is required to be consistent with the SS-OCT scanning position and to avoid eyelids, eyelashes and hair occlusion. Dark areas are avoided in the image, and the image quality is not less than 90. This item is optional for children under 6 years old.

3.4.2.12 Wide angle OCT/OCTA (Zeiss-9000) Wide-angle OCT/OCTA examinations were performed after cycloplegia. OCT/OCTA location：macular + optic disc area. Shooting mode: 12*12mm, 15*9mm angio mode; 16mm loop sweep mode (horizontal and vertical directions) a total of 8 scans. Shooting requirements: communicate more with the subject; the forehead and chin must be close to the instrument. If the image quality is affected by blinking or eye movement during shooting, participants need to re-shoot. This item is optional for children under 6 years old.

3.4.3 Questionnaire: The questionnaire is about the time children spend on outdoor activities and near work.

4. Follow up

4.1Frequency: Combined use of 1% atropine and 0.01% atropine group is followed up after first week, then every three months. 0.01% atropine group is followed up every three months.

4.2 Examinations:

4.2.1 First week follow up for combined use group: accommodation, near vison acuity > mesopic pupil size > Autorefraction and subjective refraction > IOL-Master, Pentacam, Swept-source optical coherence tomography（SS-OCT，Topcon), wide-angle optical coherence tomography angiography(OCTA,Zeiss-9000

4.2.2 Every three months: accommodation, near vison acuity > mesopic pupil size > slit lamp anterior segment examination > cycloplegia > Autorefraction and subjective refraction > IOL-Master, Pentacam, Swept-source optical coherence tomography（SS-OCT，Topcon), wide-angle optical coherence tomography angiography(OCTA,Zeiss-9000

5. Statistical Analysis

5.1 Descriptive statistics A．Continuity variables: sample size, mean, standard deviation, minimum, maximum, quartile B．Classification variable or grade variable: frequency distribution

5.2 statistical methods A. Continuous variables: The normality test uses the Kolmogorov-Smirnov test. If the normal distribution is satisfied, the t test or one-way ANOVA is used; if the normal distribution is not satisfied, the Mann-Whitney U test or the Kruskal Wallis test is used. The two-two comparison between groups was performed using the Bonferroni method. B. Categorical variable: chi-square test. C. Correlation analysis:

simple linear regression and stepwise multiple linear regression, using nonlinear regression if necessary.

5.3 Statistical significance All differences were statistically defined as $P < 0.05$ (bilateral)

5.4 Subgroup analysis Subjects will be assigned to different subgroups for subgroup analysis based on age, gender, diopter, axial length, fundus structure, and functional changes.

5.5 Interim analysis Baseline data (2019) and follow-up data are used for analysis and reporting.

6. Ethical issues

6.1 Ethics committee The study will be carried out after the approval of the Shanghai General Hospital Ethics Committee and strictly abide by the Helsinki Declaration.

6.2 Protect the privacy of participants In order to protect the privacy of the children and adolescents in the test, when the research materials are provided to other organizations, the subject code or initials should be used instead of their ID number or real name. In addition, the researcher and the relevant staff involved in the research must keep the privacy information of the children and adolescents in the test confidential.

6.3 Informed consent The informed consent form will be distributed to the children and adolescents participating in the study and their parents or guardians after approval by the ethics committee. For children and adolescents and their parents or guardians who voluntarily agree to participate in the study, parents or guardians are required to sign an informed consent form prior to the baseline study. Before signing the informed consent form, the researcher should fully introduce the content of the study, the benefit of the subject and the potential risks, and confirm that the children and adolescents and their parents or guardians fully understand and voluntarily sign the informed consent form. When signing the informed consent form, the parent or guardian has sufficient time to consider and has the right to ask questions. For questions from parents or guardians, the researcher needs to provide adequate answers. For parents or guardians who agree to sign an informed consent form, the investigator signs the informed consent form after the informed consent is fully explained and states the relationship with the child and adolescent. Informed consent is in duplicate, one of which is kept by the parent or guardian and the other is kept by the researcher. During the research process, if there is a major change in the research content, the revised informed consent form should be sent to the ethics committee for approval. After the approval, the researcher must fully communicate with the children and adolescents and their parents or guardians, and confirm that they agree to continue to participate in the study and re-sign the informed consent form.

7. Funds and insurance funds

Before the start of the study, funds were raised by the Shanghai Eye Disease Prevention and Treatment Center.

8. References

[1] impairment: 2010. Br J Ophthalmol. 2012 ,96:614-8.

[2] Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. Ophthalmic Physiol Opt 2012; 32: 3–16.

[3] He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern china. Invest Ophthalmol Vis Sci. 2004,45:793-9.

[4] Wu JF, Bi HS, Wang SM, et al.Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study.PLoS One. 2013 , 23;8:e82763.

[5] Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. Ann Acad Med Singapore. 2004;33:27-33.

[6] Morgan IG, Ohno-Matsui K, Saw SM. Myopia. Lancet. 2012，379:1739-48.

[7] Xu L, Wang Y, Li Y, Wang Y, Cui T, Li J, Jonas JB. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. Ophthalmology. 2006;113:1134.e1-11.

[8] Liang YB, Friedman DS, Wong TY, et al.Prevalence and causes of low vision and blindness in a rural chinese adult population: the Handan Eye Study. Ophthalmology. 2008;115:1965-72.

[9] He X, Zhao R, Sankaridurg P, Zhu J, Naduvilath T, Ma Y, Lu L, Lv M, Smith EL 3rd, Resnikoff S, Naidoo K, Zou H, Xu X. Design and methodology of the Shanghai child and adolescent large-scale eye study (SCALE). Clin Exp Ophthalmol. 2017 Sep 12. doi: 10.1111/ceo.13065. [Epub ahead of print].

[10] Cheng SC, Lam CS, Yap MK. Prevalence of myopia-related retinal changes among 12-18 year old Hong Kong Chinese high myopes. Ophthalmic Physiol Opt. 2013 ;33:652-60.

[11] Zhang M, Wang J, Pechauer AD, Hwang TS, Gao SS, Liu L, Liu L, Bailey ST, Wilson DJ, Huang D, Jia Y. Advanced image processing for optical coherence tomographic angiography of macular diseases. Biomed Opt Expres. 2015;6(12):4661-75.

[12] Ferrara D, Waheed NK, Duker JS. Investigating the choriocapillaris and choroidal vasculature with new optical coherence tomography technologies. Prog Retin Eye Res. 2016;52: 130-55.

[13] Li M, Yang Y, Jiang H, Gregori G, Roisman L, Zheng F, Ke B, Qu D, Wang J. Retinal microvascular network and microcirculation assessments in high myopia. Am J Ophthalmol. 2017;174:56-67.

[14] Yang Y, Wang J, Jiang H, Yang X, Feng L, Hu L, Wang L, Lu F, Shen M.Retinal Microvasculature Alteration in High Myopia. Invest Ophthalmol Vis Sci. 2016;57(14):6020-6030.

[15] Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol. 2008;146:496-500.

[16] Fujiwara T, Imamura Y, Margolis R, Slakter JS, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. Am J Ophthalmol. 2009;148:445-50.

[17] Ho M, Liu DT, Chan VC, Lam DS. Choroidal thickness measurement in myopic eyes by enhanced depth optical coherence tomography. Ophthalmology. 2013;120:1909-14.

[18] Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol. 2009;147:811-5.

[19] Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. Invest Ophthalmol Vis Sci. 2010 ;51:2173-6.

[20] Nishida Y, Fujiwara T, Imamura Y, Lima LH, Kurosaka D, Spaide RF. Choroidal thickness and visual acuity in highly myopic eyes. Retina. 2012;32:1229-36.

[21] Flores-Moreno I, Lugo F, Duker JS, Ruiz-Moreno JM. The relationship between axial length and choroidal thickness in eyes with high myopia. Am J Ophthalmol. 2013 ;155:314-319.

[22] He J, Lu L, He X, et al. The Relationship between Crystalline Lens Power and Refractive Error in Older Chinese Adults: The Shanghai Eye Study. PLoS One. 2017;12(1):e0170030.

[23] Yokoi T, Jonas JB, Shimada N,et al. Peripapillary Diffuse Chorioretinal Atrophy in Children as a Sign of Eventual PathologicMyopia in Adults. Ophthalmology. 2016;123(8):1783-7.

[24] Kyoko Ohno-Matsui, Timothy Y.Y. Lai, Chi-Chun Lai, ,et al.Updates of pathologic myopia. Progress in Retinal and Eye Research. 2016; 52: 156-87.

[25] Pavan Kumar Verkicharla1, Kyoko Ohno-Matsui2 and Seang Mei Saw.Current and predicted demographics of high myopia and an update of its associated pathological changes. Ophthalmic & Physiological Optics. 2015; 35(5): 465–475.

[26] Jonas JB, Jonas SB, Jonas RA, Holbach L, Dai Y, Sun X, Panda-Jonas S. Parapapillary atrophy: histological gamma zone and delta zone. PLoS One.2012;7(10): e47237.

[27] Dai Y, Jonas JB, Huang H, Wang M, Sun X. Microstructure of parapapillary atrophy: beta zone and gamma zone. Invest Ophthalmol Vis Sci. 2013;54(3): 2013-8.

[28] Kim TW, Kim M, Weinreb RN, Woo SJ, Park KH, Hwang JM. Optic disc change with incipient myopia of childhood. Ophthalmology, 2012; 119(1):21-6.e1-3.

[29] Fledelius HC, Goldschmidt E. Optic disc appearance and retinal temporal vessel arcade geometry in high myopia, as based on followup data over 38 years. Acta Ophthalmol.2010;88(5): 514-20.

[30] Rong SS, Chen LJ, Pang CP. Myopia Genetics-The Asia-Pacific Perspective. Asia Pac J Ophthalmol (Phila). 2016;5(4):236-44.

[31] 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(2):391-9.

[32] Pineles SL, Kraker RT, VanderVeen DK, Hutchinson AK, Galvin JA, Wilson LB,Lambert SR. Atropine for the Prevention of Myopia Progression in Children: A Report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(12):1857-1866.

[33] Tan D, Tay SA, Loh KL, Chia A. Topical Atropine in the Control of Myopia. Asia Pac J Ophthalmol (Phila). 2016 Nov/Dec;5(6):424-428.

[34] McBrien NA, Stell WK, Carr B .How does atropine exert its anti-myopia effects?. Ophthalmic Physiol Opt. 2013 ;33:373-8.

[35] Lin HJ, Wan L, Chen WC,et al .Muscarinic acetylcholine receptor 3 is dominant in myopia progression. Invest Ophthalmol Vis Sci. 2012;53:6519-25.

[36] Hung LF, Arumugam B, Ostrin L, Patel N, Trier K, Jong M, Smith EL III. The Adenosine Receptor Antagonist, 7-Methylxanthine, Alters Emmetropizing Responses in Infant Macaques. Invest Ophthalmol Vis Sci. 2018;59(1):472-486.

[37] Trier K, Munk Ribel-Madsen S, Cui D, Brøgger Christensen S. Systemic 7-methylxanthine in retarding axial eye growth and myopia progression: a 36-month pilot study. J Ocul Biol Dis Infor. 2008;1(2-4):85-93.

[38] Chen X, Xue A, Chen W, Ding Y, Yan D, Peng J, Zeng C, Qu J, Zhou X. Assessment of exonic single nucleotide polymorphisms in the adenosine A2A receptor gene to high myopia susceptibility in Chinese subjects. Mol Vis. 2011;17:486-91.