Atropine 0.01% eye drops to control myopia progression in Chinese children: a randomized, double-masked, placebo-controlled clinical trial

Trial Protocal

Research Question:

1. Does atropine 0.01% eye drops prevent myopia progression and axial elongation when compared with the placebo group in Chinese myopic children?
2. Do the adverse effects of atropine 0.01% eye drops support its use in children with myopia?

Rationale:

Myopia has become a critical public health problem among both children and adults, especially in some East and Southeast Asian countries such as China and Singapore.[1,2] Recent review predicted that approximately half of the world's population will have myopia by 2050 and with 10% being high myopia.[3] In China, the prevalence of myopia reaches nearly 70% in grade 7 students, and exceeds 80% in university students.[4,5] Myopia not only is the most common causes of avoidable visual impairment and blindness, but high or pathologic myopia is associated with increased risk of irreversible blinding conditions, including myopic retinopathy, retinal detachment, choroidal neovascularization, and glaucoma,[6-9] leading to a heavy cost burden on individuals and communities.[10,11]

Atropine is a nonspecific muscarinic receptor antagonist. The exact mechanism of topical atropine in slowing myopia progression is still not clearly understood so far. The receptors was initially thought to be in the ciliary muscle by inhibiting the excessive accommodation, but atropine is effective in preventing myopia in animals, in which ciliary muscle is mediated by nicotinic receptor rather than muscarinic receptors.[12-14] However, atropine might have biochemical effects based on the retinal site of action, and muscarinic antagonist control of myopia is mediated via M1 and M4 muscarinic receptors.[15] Moreover, an inhibition of atropine on the synthesis of glycosaminoglycan in scleral chondrocytes may also exert anti-myopia effects.[16,17] At present, topical atropine has been demonstrated to have the strongest clinical effect on slowing the progression of myopia.[18-20] In 2006, the Atropine for the Treatment of Myopia 1 (ATOM 1) study founded that the mean rate of myopia progression after 2 years was only -0.28±0.92 D in the atropine 1% group compared with -1.20±0.69 D in

the placebo group.[19] However, ocular side effects induced by 1% atropine such as blurred near vision, photophobia cycloplegia and allergy have limited its use. Furthermore, there was a greater myopic rebound in eyes that had received 0.5% and 0.1% atropine when atropine was stopped (ATOM 2 study), whereas those receiving a low-dose 0.01% concentration proved sustained and minimal change.[21] Therefore, low concentration of 0.01% atropine is increasingly applied to clinical treatment for myopic children in Asia.

At present, the majority of the studies have been performed to evaluate the efficacy and safety of low concentration of 0.01% atropine through retrospective studies,[22-24] but few data are available from randomized controlled trials, with the exception of one in Singapore (ATOM 2 study).[20] In the ATOM 2 study in Singapore, Chia et al. reported the mean myopic progression over 2 years in the 355 children was -0.30±0.60 D, -0.38±0.63 D, and -0.49±0.63 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively.[20] However, the lack of a placebo control group was an acknowledged weakness of the study. Thus, the effect of low concentration of 0.01% atropine has not been extensively evaluated through placebo-controlled trial at present.

Through randomized controlled trial, it can explore the efficacy of 0.01% low-concentration atropine eye drops in retarding the progression of myopia in school-aged children in China, as well as the side effects and adverse reactions, which help answer the above questions.

Objective:

1. To explore the effect of 0.01% low-concentration atropine eye drops on the myopia progression and axial elongation in low and moderate myopic Chinese children;
2. To explore the side effects and adverse effects of 0.01% low-concentration atropine eye drops in low and moderate myopic Chinese children;
3. To explore the myopic rebound when 0.01% low-concentration atropine eye drops was stopped;

4. To explore the optimal age for 0.01% low-concentration atropine eye drops use;

Hypothesis:

0.01% atropine eyed rops can significantly slow the myopia progression and axial elongation in children.

Study Plan

Design:

The design is a randomized, double-masked, placebo-controlled trial aimed to investigate the efficacy and safety of low concentrations of 0.01% atropine in low and moderate myopic children from April 2018 to July 2020. Two phases will include in this study. All children will be recruited and randomized to receive either 0.01% atropine or placebo eye drops in both eyes once daily at an allocation ratio of 1:1 for one year in Phase 1. At the beginning of the second year, the 0.01% atropine group will be crossed over to the placebo group and the placebo group will be crossed over to the 0.01% atropine group for one year in Phase 2.

Inclusion and Exclusion Criteria:

The myopic children will be recruited from Beijing Tongren Hospital, Beijing, China, between April 2018 and July 2018. All subjects met the following inclusion criteria:

1. Children aged 6 to 12 years with refractive error of spherical equivalent (SE) range of -1.00 D to -6.00 D in both eyes;
2. Astigmatism of -1.50 D or less in both eyes;
3. Best-corrected distance visual acuity 0.20 logMAR or better in both eyes;
4. Intraocular pressure (IOP) of less than 21 mm Hg.

Exclusion criteria were as follows:

1. Children with other combined ocular diseases (e.g., amblyopia, strabismus, corneal scar, cataract, glaucoma, or ocular tumor);
2. Previous or current treatment with atropine, pirenzepine, contact lenses, bifocals, or progressive addition lenses for myopia, allergy to atropine, cyclopentolate, or excipients.

Procedures:

All children who meet the inclusion and exclusion criteria will be referred to the clinic study coordinator who will seek fully informed patient consent prior to enrolling the patient. Those enrolled will be participated in this study underwent the same, standardized examination procedure at the baseline visit and 6 and 12 months after initiation of visit. Cycloplegic refraction was measured by an autorefractor (HRK7000 A; Huvitz, Gunpo, South Korea) with three times consecutively with average data used for analysis. All 3 readings should be at most 0.25 D apart in both the spherical and cylinder components. During the examination of each subject, 3 drops of 1% cyclopentolate (Alcon) were administered at a 5-minute interval. Thirty minutes after the last drop, if pupillary light reflex was still present or the pupil size was less than 6.0 mm, a fourth drop of 1% cyclopentolate was administered and the examination was repeated 15 minutes later. Axial length (AL) was measured using the Lenstar LS900 (Haag-Streit Koeniz, Switzerland) with five readings were taken and averaged. A non-contact tonometer (HNT-7000, Huvitz, Gunpo, South Korea) was used to measure the intraocular pressure with three repeated measurements. Additionally, a detailed interviewer-administered questionnaire answered by parents was used to collect the information of their children on the age of myopia onset, number of myopic parents, time near work and outdoors activities (hr/day) after school hours. Subjects were given a calendar to mark out the days when the trial medications were used and with more than 80% compliance rate were considered to include in the results analysis. Children were also provided photochromatic glasses (which darken

on exposure to ultraviolet or sunlight) if they experienced glare or if their parents were worried of excessive light exposure, or progressive glasses (reading add) if they experienced difficulty with near vision.

Sample size estimates:

Sample size was calculated based on the results from the previous studies.[18, 19, 23] We assume that 0.01% atropine reduces the myopia progression rate by at least -0.36 D with standard deviation of 0.70 D, assuming a power of 90% with a 2-sided test of 5%. Thus, this study required 80 subjects in each group. Considering a drop-out rate of 25%, a total of 220 participants would be adequate.

Randomization and Masking

With the schedule generated by SAS program (SAS Institute, Cary, NC, USA), a statistician operated the randomization independently. Every eligible four children were randomly allocated into the intervention group or control group according to the priority order the children visited the hospital for treatment. The participants had an equal probability of assignment to either the two groups. The 0.01% atropine and placebo eye drops were packaged in identical bottles, and thus investigators and participants were not able to identify the contents. There were only the expiration date and study number on the bottle. The data analysts were also blinded to minimize observational bias.

Ethical consideration:

Informed written consent was obtained from at least one parent, as well as verbal assent from each child. This clinical trial adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Beijing Tongren

Hospital, Capital Medical University.

Benefits of study:

A high prevalence of 83.2% for myopia and 11.1% for high myopia was reported for central Chinese university students. Thus, the prevention and retardation of myopia progression will both statistically and clinically significant in children to reduce sight-threatening complications associated with myopia in later life.

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Statistical Analysis Plan

Data preparation

All examination data were independently entered twice into a database using commercial software (Epidata software 3.1; The Epidata Association, Odense, Denmark) by two independent individuals. When there were discrepancies between the database entries, the raw data were checked. Statistical software (SAS version 9.4; SAS, Inc., Cary, NC, USA) was used for cleaning, logically checking, merging data, and analysis.

Outcomes

The spherical equivalent (SE) was calculated as the dioptric powers of the sphere and half of the cylinder (sphere + 0.5 × cylinder). The primary outcome was myopia progression and axial elongation defined as the mean change in cycloplegic SE and AL over 1 year. The secondary outcomes included adverse events during the treatment.

Statistical analysis

For all analyses, SPSS version 20.0 (SPSS, Chicago, Illinois, USA), was used. For continuous variables, the independent t-test and analysis of covariance were used to determine statistical significance between the atropine and control groups. The chi-square tests were used to compare the categorized data. We will first compare the demographics and baseline characteristics between 0.01% atropine and placebo groups, such as age, sex, initial SE (D), initial AL (mm), age at myopia onset, parental myopia, time outdoors and near work. We will examine the differences in the mean values of myopia progression and axial elongation between the atropine and control groups. In order to explore potential risk factors, including age at baseline, sex, initial spherical equivalent, intraocular pressure, age at myopia onset, parental myopia, time outdoors, and near work, associated with progressors in 0.01% atropine group, the multiple log-binomial regression analysis was performed using those factors as the dependent variable. Analyses were only performed on the right eye.

0.01%阿托品滴眼液对中国学龄儿童近视进展影响的随机双盲对照试验

计划书

研究问题：

1. 与安慰剂组相比，0.01％阿托品滴眼液能否有效延缓中国近视儿童的近视进展和眼轴延长？

2. 由于 0.01％阿托品滴眼液能够引起一定的不良反应，能否在中国近视儿童中使用？

研究背景

近视已经成为影响儿童和成人眼健康的重要公共卫生问题，尤其在一些东亚和东南亚国家，例如中国和新加坡[1,2]。最近的研究预测，到 2050 年全球约有一半人口将患有近视，其中 10％是高度近视[3]。在中国，七年级学生的近视患病率达到近 70％，在大学生中甚至超过 80％[4,5]。近视不仅是可避免的视力残障和盲的最常见原因，且病理性近视会增加不可逆性致盲眼病的风险，包括近视性视网膜病变，视网膜脱离，脉络膜新生血管和青光眼[6-9]，这会给个人和社会带来沉重的成本负担[10,11]。

阿托品是一种非特异性毒蕈碱受体拮抗剂。到目前为止，尚不清楚阿托品延缓近视进展的确切机制。最初认为该受体通过抑制睫状肌的过度调节，但一些动物的睫状肌是由烟碱受体而非毒蕈碱受体介导，阿托品仍可有效预防动物的近视[12-14]。然而，阿托品可能作用于 M1 和 M4 毒蕈碱受体调节视网膜上的作用部位，从而毒蕈碱拮抗剂可控制近视[15]。此外，阿托品对巩膜软骨细胞糖胺聚糖合成的抑制作用也可能发挥延缓近视进展的作用[16,17]。目前，在临床实验中已证明阿托品有很好的减缓近视的进展的效果[18-20]。2006 年，阿托品治疗近视（ATOM 1）的研究发现，使用 1%阿托品 2 年后的平均近视进展仅为-0.28±0.92 D，而安慰剂组为-1.20±0.69D[19]。然而，1％阿托品引起的眼部不适如近视模糊、畏光、过敏，限制了其使用。此外研究发现，停用 0.5％和 0.1％阿托品滴眼液后近视度数的反弹更大（ATOM 2 研究），而接受低浓度 0.01％阿托品滴眼液组的反弹效应较小[21]。因此，低浓度 0.01％阿托品滴眼液被越来越多地用于亚洲近视儿童的临床应用。

目前，大多数研究都是通过回顾性研究来评估低浓度 0.01%阿托品的疗效和安全性[22-24]，但很少有来自随机对照试验的数据，除了新加坡的一项研究（ATOM 2）[20]。Chia 等人在新加坡进行的 ATOM 2 研究中，在 355 名儿童中，使用 0.5%，0.1%和 0.01%阿托品滴眼液组的 2 年平均近视进展分别为-0.30±0.60 D，-0.38±0.63 D 和-0.49±0.63D[20]。但是，缺乏安慰剂对照组是该研究公认的不足。因此，目前尚未通过安慰剂对照试验广泛评估低浓度 0.01%阿托品滴眼液对中国儿童的效果。

因此，通过随机对照试验可以探索 0.01%阿托品滴眼液在中国学龄儿童延缓近视进展中的作用以及副作用，从而有助于回答上述问题。

研究目的

1. 分析 0.01%阿托品滴眼液对中国学龄儿童延缓近视进展和眼轴延长的效果；
2. 分析 0.01%阿托品滴眼液对中国学龄儿童的不良反应；
3. 分析停用 0.01%低浓度阿托品滴眼液后的反弹效应；
4. 探索低浓度阿托品在学龄儿童中使用的最佳年龄；

研究假设

0.01%阿托品滴眼液可以显著减慢近视儿童的近视进展和眼轴伸长。

研究计划

设计

该研究是一项随机、双盲、安慰剂对照试验，旨在探索 0.01%阿托品滴眼液在中低度近视儿童中的效果和安全性，该研究于 2018 年 4 月至 2020 年 7 月进行。本研究将包括两个阶段：在第 1 阶段中，将招募的所有儿童按照 1:1 的比例随机分配到 0.01%阿托品滴眼液或安慰剂组，为期一年；第二年时，0.01%阿托品滴眼液组将在第二阶段转入安慰剂组，而安慰剂组将转入 0.01%阿托品滴眼液组，为期一年。

纳入和排除标准

所有近视儿童将在 2018 年 4 月至 2018 年 7 月之间从北京同仁医院招募。所有受试者均符合以下入选标准：

(1). 6~12 岁学龄儿童，双眼等效球镜在-1.00 D 至-6.00 D 之间；

(2). 双眼中任何一眼散光小于或等于 1.50 D；

(3). 双眼的最佳矫正视力至少为 0.20 logMAR；

(4). 双眼眼压小于 21 mm Hg；

排除标准：

(1). 患有其它眼部疾病（例如弱视，斜视，角膜疤痕，白内障，青光眼或眼部肿瘤等）的儿童；

(2). 对阿托品和环戊酸酯或赋形剂过敏的孩子，及以前或目前使用阿托品，吡仑西平，角膜接触镜，双焦点眼镜或渐进镜的孩子。

研究流程

所有符合入选和排除标准的孩子都将被转交给临床研究协调员，他们将在招募患者之前获得家长和孩子的知情同意。入组者将在基线时以及实验开始后的 6 个月和 12 个月时接受相同的标准化的检查。使用自动验光仪（HRK7000 A；韩国）连续 3 次测量睫状肌麻痹后屈光度，并使用平均值数据进行分析。球镜和柱镜的所有三个读数之间的最大差异为 0.25D。在每个受试者的检查过程中，睫状肌麻痹的方法为：每隔 5 分钟滴眼 3 次 1%的环戊通（Alcon），最后一次滴眼后 30 分钟，如果仍然存在瞳孔对光反射或瞳孔大小小于 6.0 mm，则应第四次滴入 1%环戊通，并在 15 分钟后重复检查。使用 Lenstar LS900（瑞士 Haag-Streit Koeniz）测量轴长长度（AL），五个读数并取平均值。使用非接触式眼压计（HNT-7000，韩国）通过三次重复测量来测量眼内压。此外，还使用了由父母回答的详细的问卷调查表，以收集其子女的有关近视眼发病年龄，近视父母的数量，近距离工作时间和户外活动时间（小时/天）的信息。给予受试者日历以标明使用试验药物的日期，并认为结果分析中包含 80%以上的依从率。如果儿童感到眩光或父母担心过度暴露于光线下，还可以给他们提供变色眼镜（在暴露于紫外线或日光下会变黑），或者如果他们在视近上有困难，还可以配戴渐进眼镜。

样本量的估算

根据既往研究结果[18, 19, 23]，期望用药两年后两组之间的屈光度进展量差别在

0.36 D 以上有意义，标准差为 0.70 D，把握度为 90%，则样本量为：N=2*（1.96+1.28）^{2}*(0.7) ^{2}/(0.36) ^{2}=80，考虑到 25%失访率，最终纳入 220 例受试者。

随机和双盲

根据 SAS 程序（美国北卡罗来纳州卡里市 SAS 研究所）生成的随机表，统计师独立进行随机操作。根据孩子们到医院就诊的顺序，将每 4 位合格的儿童随机分配到干预组或对照组。0.01％阿托品滴眼液和安慰剂滴眼液包装在同样的瓶中，因此研究人员和参与者无法识别其中的内容物。瓶子上只有有效日期和研究编号。

伦理道德

至少要征得一位父母的知情同意，签写知情同意书，并要征得每个孩子的口头同意。该临床试验遵守循赫尔辛基宣言的宗旨，并得到首都医科大学附属北京同仁医院伦理委员会的批准。

研究意义

据报道，中国中部大学生的近视患病率已达 83.2％，高度近视患病率为 11.1％。因此，在儿童青少年中延缓近视进展将具有重要意义，并减少与近视相关的眼底并发症。

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统计分析计划

数据准备

所有检查结果的数据均由两个独立的人使用软件（Epidata 软件 3.1）独立两次输入数据库。当数据库条目之间存在差异时，将检查原始数据。使用统计软件（SAS 版本 9.4； SAS 公司，美国北卡罗来纳州卡里）进行数据的清理，逻辑检查，合并数据和分析。

结果

等效球镜度（SE）计算方法为球体加上二分之一的柱镜（球镜度+ 0.5×柱镜度）。主要结果为近视进展和眼轴延长，定义为一年之间睫状肌麻痹后屈光度和眼轴长度的平均变化。次要结果包括实验期间的不良反应。

统计分析

对于所有分析，均使用 SPSS 20.0 版进行（SPSS，美国伊利诺伊州芝加哥）。对于连续变量使用独立样本 t 检验和协方差分析来确定 0.01％阿托品和对照组之间的统计学显着性。卡方检验用于比较分类数据。我们将首先比较 0.01％阿托品和安慰剂组的人口统计学和基线特征，例如年龄，性别，初始屈光度（D），初始眼轴长度（mm），近视发作年龄，父母近视，户外活动时间和近距离工作时间。我们将分析 0.01％阿托品组与对照组之间近视进展和眼轴延长平均值的差异。为了探讨潜在的与 0.01％阿托品组的近视进展者的危险因素，包括基线时的年龄，性别，初始屈光度，眼内压，近视发作的年龄，父母近视，户外活动的时间和近距离工作时间等，采用了多重 log-binomial 回归分析。所有分析仅纳入右眼。