Effect of plum-blossom needling versus tropicamide eye drops on adolescent myopia: protocol for a randomized crossover trial

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Abstract

OBJECTIVE: Myopia is the most common eye problem and affects an estimated 28.3% of the global population. Its incidence is increasing annually. Myopia treatment is limited to correcting visual acuity. Acupuncture is one of the main therapies in traditional Chinese medicine and includes plum-blossom needling, which has been widely used for both the prevention and treatment of adolescent myopia. We hypothesized that plum-blossom needling would be effective in treating myopia compared with a tropicamide eye drops control.

METHODS: This is a crossover randomized controlled trial involving adolescents with myopia. Participants will be randomized 1:1 to plum-blossom needle or tropicamide eye drops arms. Subjects in each arm will be treated for 20 d, followed by a 1-month washout period and treatment change for another 20 d. The primary outcome is uncorrected distance and cycloplegic refractive errors. The secondary outcomes comprise corneal curvature, lens thickness, axial length, ciliary body thickness, accommodation amplitude, the NRA/PRA (negative/positive relative accommodation), flexible adjustment, and near point of convergence. The outcome measures will be assessed at baseline, after the first treatment course (the first month), at the end of the washout period (the second month), after the second treatment course (the third month), and at follow-up (the sixth month).

DISCUSSION: The results of the trial will help to provide evidence for the efficacy of plum-blossom needling for myopia in China.

Trial registration: The study was prospectively registered on March 31, 2017 (http://www.clinicaltrials.gov; unique identifier: NCT03097198).

Keywords: Myopia; Plum-blossom needle; Tropicamide; Ophthalmic solutions; Crossover studies; Clinical protocols

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INTRODUCTION

Myopia, also known as short-sightedness or near-sightedness, is an eye condition in which light focuses in front of, instead of on, the retina. This causes distant objects to be blurry and close objects to appear normal. Other symptoms may include headaches and eye-strain. The underlying mechanism involves the length of the eyeball growing too long or, less commonly, the lens being too strong. Myopia is not among the top three causes of blindness worldwide; however, the disorder affects global health because of its complications, such as cataract, glaucoma, chorioretinal abnormalities, visual impairment, and blindness.

Myopia is the most common eye problem and is estimated to affect 28.3% of the global population; its incidence is increasing annually. You et al. reported a myopia prevalence rate of 57% in schoolchildren in Beijing aged 7-18 years in 2012, and the prevalence rate was 80.7% in children aged 16-18 years. In Hong Kong, the prevalence rate in 12-year-old was 61.5%. In Australia, the incidence of myopia is 14.4% in children under 12 years old and 29.6% in children aged 12 years and over. There is a high incidence of myopia in China, and some scholars have suggested that myopia onset occurs at a younger age in China than in other countries. Various social and economic costs are associated with this condition; during 1999-2002, the annual direct costs of myoprophylaxis were at least 3.8 billion USD in the United States. The World Health Organization has reported that, in addition to public health concerns and the costs of myopia, uncorrected visual impairment may hinder education and employment opportunities, reduce productivity, and impair quality of life.

Current treatment of myopia mainly involves optical correction, excimer laser surgery, corneal orthopedic glasses, and drugs. Owing to dynamic changes in refractive status in teenagers, excimer laser surgery is not suitable for this population. In addition, the long-term curative effect of surgery is uncertain and may even lead to complications such as corneal infection. Moreover, the curative effect of corneal orthopedic lenses and progressive multifocal glasses has not yet been determined, and they cannot effectively treat myopia and suppress myopia progression. Commonly used myopic drugs comprise M receptor antagonists, including atropine and tropicamide. The latter can inhibit increases in axial length and relax ciliary muscles to slow the progression of myopia. However, the existence of inevitable side effects, such as dilated pupils, photophobia, blurred near vision, allergic dermatitis, and systemic reactions, limit the use of tropicamide in a wide range of applications.

Acupuncture is one of the main therapies in traditional Chinese medicine and has been widely used for both the prevention and treatment of diseases for over 3000 years. Plum-blossom needling is a type of acupuncture that involves shallow puncturing with multiple needles. A curative effect is obtained by stimulating superficial parts of the body and the method generally produces no adverse reactions. Results from several randomized clinical trials have shown that stimulating specific acupoints with plum-blossom needles may be an effective treatment for adolescent myopia. However, convincing evidence of the effectiveness of this therapy remains inadequate owing to the poor quality of current study designs. Therefore, we aim to conduct a crossover randomized controlled trial to address these problems and hopefully provide a more conclusive answer to the question of whether plum-blossom needling is effective for myopia.

METHODS

Study design

This study is a crossover randomized controlled clinical trial in which each subject will complete two interventions (plum-blossom needling and tropicamide eye drops) with a washout period of 1 month between each trial. The order will be determined using a randomization sequence with a 1:1 ratio. The study flow is illustrated in Table 1.

This study will be conducted in accordance with the Declaration of Helsinki (last amended 2013). The study has been approved by the regional research ethics committee of the The Eye Hospital of Wenzhou Medical University (approval No. KYK [2016] 19). All patients will be required to provide written informed consent before inclusion in the study.

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). A SPIRIT checklist is provided in the Additional file.

Participants

Recruitment: patients will be recruited from The Eye Hospital of Wenzhou Medical University.

Inclusion criteria: participants will be included if they fulfilled the following conditions: aged between 8 and 20 years old; diagnosed with myopia, the dioptr spherical lenses must be ≤ −3.00 D, as measured under cycloplegia; both guardians and subjects provided a signed written consent form.

Exclusion criteria: patients with any of the following conditions will be excluded: diopter spherical lenses > −3.00 D, or uncorrected distance visual acuity < 0.1, or pathologic myopia with eye complications; diopter spherical lens ≥ 1.50 D or cylindrical lenses ≥ 1.00 D, as measured under cycloplegia; other diseases of the affected eyes that would hinder the assessment of acupuncture efficacy; subjects with serious systemic diseases, such as cerebrovascular, liver, kidney, hematopoietic system, and psychiatric diseases; ongoing long-term use of other related drugs or treatments; parents or subjects refusal to participate in the trial; participating in other
ongoing clinical trials.
Withdrawal and termination criteria: patients with any of the following conditions will be withdrawal or terminate and researchers should record the reasons and timing of the withdrawal: subject experiences severe adverse reactions that suggest discontinuation of participation; subject experiences serious complications or a worsening condition that requires emergency measures; subject proposes withdrawal from the study; subject does not cooperate (i.e., does not follow the treatment after it has been repeatedly explained by the clinician).

Randomization and allocation
After completion of enrollment, patients will be randomly allocated to plum-blossom needle or tropicamide eye drops arms. A stratified complete block randomization method will be used in this trial. The randomization scheme will be generated using random number formulae in Microsoft Excel. Only those individuals who will collect or analyze clinical data can be blinded. Double masking will be used (Investigator, Outcomes Assessor).

Intervention
Participants will be randomized 1:1 to plum-blossom needle or tropicamide eye drops arms. Subjects in each arm will be treated for 20 d, followed by a 1-month washout period and a treatment change for another 20 d. The washout periods for both treatments are 1 month. Group A will first receive one course of treatment with a plum-blossom needle, and then one course of eye drops after the washout period. Group B will first receive one course of treatment using eye drops, and then one course of treatment with a plum-blossom needle after the washout period (Figure 1).

Plum-blossom needling group
Acupoint selection and location (Figure 2): Zhengguang 1: on the head, at the junction of the medial one-fourth and lateral three-fourths of the supraorbital arch between the supraorbital ridges and the eyebrows. 98 subjects with myopia were randomized to either the plum-blossom needle or tropicamide eye drops group. The washout period is 1 month.
bital rim, at the midpoint between Cuanzhu (BL 2) and Yuyao (EX-HN 4).
Zhengguang 2: On the head, at the junction of the medial three-fourths and lateral one-fourth of the supraorbital rim, at the midpoint between Sizhukong (TE 23) and Yuyao (EX-HN 4).
Fengchi (GB 20): In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of the sternocleidomastoid and trapezius muscles.17
Dazhui (GV 14): In the posterior region of the neck, in the depression inferior to the-spinous process of the seventh cervical vertebra (C 7), on the posterior median line.17
Hegu (LI 4): On the dorsum of the hand, radial to the midpoint of the second metacarpal bone.17

Selection of needling instruments: Double-head dermal needles (HWATO, Suzhou, China), which tips were removed with sandpaper. (Figure 3).
Tropicamide eye drops 6 mL: 30 mg (Bausch & Lomb, Shandong, China).
Plum-blossom needle manipulation methods: after the skin has been wiped with 75% alcohol, plum-blossom needles will be tapped perpendicularly on the skin at the selected acupoints using wrist force and then lifted immediately. Each point will be tapped repeatedly for 20 to 50 times and both sides of the cervical vertebrae, temporal region, and supra/infraborital margin will be tapped repeatedly. Acupuncturists should tap the points gently so that patients feel only a little pain and stop when the skin gets flushed but is not bleeding.
The acupuncturists are required to have a certificate.
confirming their traditional Chinese medicine practitioner qualification, to have more than 500 h of clinical practice time, and to undertake clinical-standard training on this subject. Each acupuncturist is required to operate in strict accordance with aforementioned procedures.

Course of treatment
Plum-blossom needle tapping group: subjects will receive treatment every other day; 20 d constitute one course.
Tropicamide eye drops group: One drop is administered to both eyes every night before bed; 20 d constitute one course.

General advice
Very few side effects occur following plum-blossom needle tapping or tropicamide eye drop treatment. One medication used for pupil dilation during the examination, cyclopentolate hydrochloride eye drops, may cause transient dizziness, nausea, dry mouth, burning sensation, foreign body sensation, blurred vision, photophobia, or mild conjunctiva congestion.

Outcome measures
Primary outcome: changes in uncorrected distance visual acuity: uncorrected distance visual acuity test using the international standard logarithmic visual acuity chart. The visual chart will be shown by projection; the distance between the visual chart and the subject will be 5 m. Results will be recorded in decimal numbers. Subjects who peek during the test will be avoided.
Changes in cycloplegic refractive errors: diopter examination: 40 min after the administration of cyclopentolate hydrochloride eye drops, subjective refraction (NI-DEK AOS-660) will be measured.
Secondary outcomes: corneal curvature, lens thickness, and axial length will be automatically measured using a Lenstar (LS 900, Haag-Streit Company, Switzerland). Measurements will be conducted at least three times and the mean value will be taken.
Ciliary body thickness: anterior segment OCT (SS-1000) will be applied along the radial direction to measure ciliary body thickness at 1, 2, and 3 mm from the 12 o’clock position of the eyeball to the scleral spur. Results will be recorded. Accommodation amplitude, the NRA/PRA, flexible adjustment, and near point of convergence will be measured.
The above outcome measures will be assessed before the treatment, after the first treatment course, after the washout period, after the second treatment course, and at follow-up.

Sample size
The study sample size was calculated using PASS 11 power and sample size software (NCSS Corp, Kaysville, UT, USA). The analysis indicated that a two-sided $t$-test will achieve approximately 80% power if the total sample size of a $2 \times 2$ crossover design is $n = 40$. Based on a preliminary test, we assumed that the actual mean diopter difference (as primary outcome) is 0.13, the square root of the within mean square error is 0.2, and the significance level is 0.05. Enrollment of 41 patients would provide 80% power to demonstrate a significant difference between the study arms. We expect approximately 20% loss to follow-up. To achieve the calculated statistical power, we decided to recruit 49 patients within each group. In total, 98 patients will participate in this trial. To minimize loss to follow-up, we will call the participants the day before the trial to remind them of their appointment time. We will call them again on the day after the appointment if they fail to attend on time to invite them to reschedule soon.

Statistical analysis
All analyses will be conducted by the Biostatistics Center of the Clinical Research Center at The Eye Hospital of Wenzhou Medical University. Analyses will be performed on the intention-to-treat group of participants who will have been randomized regardless of whether they receive any treatment. Missing data will be replaced according to the principle of the last observation carried forward. A variance analysis will be used to test the global hypothesis $H_0$: “There will be no difference in the success probability between the two groups.”
significance level used for the statistical analysis will be 5%; therefore, \( P < 0.05 \) will indicate significance. Analysis of variance (ANOVA) for repeated measures will be used to compare the two groups. Within-group comparisons for the outcomes at each time point will be conducted using Tukey’s post hoc test of multivariate ANOVA. The \( \chi^2 \) test will be used to analyze proportional data. Quantitative variables will be displayed as the mean ± standard deviation if normally distributed or as the median (interquartile range) if asymmetrically distributed. All analyses will be performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, New York, USA) software program (version 23.0) for Windows 10.

**DISCUSSION**

Many studies show that plum-blossom needling is effective for adolescent myopia.\(^{12,16} \) However, according to the strict criteria for clinical trials demanded by evidence-based medicine, evidence for the effectiveness of acupuncture is insufficient because of the poor quality of studies (e.g., small sample size, no description of randomization methods, no standardized acupuncture protocol), which may lead to problems such as performance bias. This trial will use a random number table, crossover design, standardized acupuncture protocol, and other randomized controlled trial design features. We aim to conduct a crossover randomized controlled trial to clarify the efficacy of plum-blossom needle treatment for treating adolescent myopia and slowing the speed of myopia progression.

Plum-blossom needling is a type of traditional Chinese acupuncture therapy. It is based on the theory of meridians and collaterals and is widely used in treating neurological, dermatological, and ophthalmic diseases. On the basis of previous clinical experience and expert opinions, in this study we will select skin regions in the neck and superciliary arch in addition to regular acupoints, such as Zhengguang, Fengchi (GB 20), Da-zhui (GV 14), and Hegu (LI 4). This combination is safe, effective, and easy to use. Although atropine is regarded as a classic therapeutic agent for the treatment of myopia,\(^{19,21} \) low-concentration atropine eye drops are not available in China, so we selected the most commonly used medication, tropicamide eye drops, as the positive control. As it is difficult to design a non-effective therapy that is similar to plum-blossom needling to blind subjects, we will use a crossover design: both groups will receive the same two types of treatment, but in a different order.

Filiform needle puncture is a classical acupuncture method. Many reports have confirmed that filiform needle puncturing has some benefits for myopia. However, the capillaries around the eye area are rich in blood vessels so it is difficult to avoid bleeding and pain during treatment, making it difficult for children and young people to conquer their fear of acupuncture. However, a plum-blossom needle resembles a small hammer with pointless short needles on it; this is tapped gently on the skin. The technique is non-invasive, so there is no bleeding and hardly any pain during treatment. For these reasons, plum-blossom needling is widely accepted by children.

School-age children are a high-risk group for myopia; previous screening surveys have shown that third grade (8 to 10 years of age) is a pivotal time for the development of myopia.\(^{20,25} \) Plum-blossom needling is effective in reversing myopia and prohibits early myopic progression; we therefore set 8 years as the lower age limit for participant inclusion. Eye development is completed by about 18 years and so the progression of myopia ceases. However, some students experience a sharp short-term decline in vision owing to the growing burden of study. Their eyesight can be partly restored after alleviating eye fatigue using plum-blossom needle treatment. Therefore, we set 20 years as the upper age limit for participant inclusion.

This study has two main outcome indicators: uncorrected visual acuity and diopter difference. Uncorrected visual acuity is one of the most intuitive and easy to monitor indicators, whereas diopter difference is a relatively objective indicator. Generally, patients with myopia can only experience corrected vision using optical methods and diopter change is not reversible. Although a few studies have reported that some therapies can improve uncorrected visual acuity, these methods cannot halt myopia progression or affect diopter increase. We therefore chose diopter difference as the main indicator of whether plum-blossom needle therapy can prevent diopter increase, and even reduce it. As the teenage eyeball is still developing, an increase in the ocular axis is inevitable, so a long-term diopter increase is also inevitable. Therefore, to compare the long-term curative effect of the treatments, we will focus on the increasing rate of diopter change.

In conclusion, the results of this trial are expected to provide evidence for the efficacy of plum-blossom needling for adolescent myopia in China.

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