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소아근시에 대한 눈 주위혈 지압의 유효성 및 안전성 평가 연구

차호열[1] · **정아람**[1] · **천진홍**[1,2] · **최준용**[3] · **김기봉**[1,2,3]

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Abstract

The Efficacy and Safety of Periocular Acupoint Stimulation on Myopia Progression in Children: A Study Protocol

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Objectives

Myopia has a higher prevalence rate in eastern countries, which also have a higher rate of educational fever compared to western countries. Considering this, social costs paid for myopia will increase rapidly in Korea. Although the development of myopia treatment is necessary, there has been a lack of relevant studies. Thus, this study aims to produce data to prevent unnecessary treatments and medical expenses.

Methods

The objective is to evaluate the effect of periocular acupressure exerted by a medical massager for myopia. This is an open-label, prospective, single-arm, and pre and post superiority study. The subjects are 7~12-year-old myopia patients with under 5 D (diopter) of spherical equivalent. A total of 56 subjects were enrolled. The selected subjects will wear the massager for 15 minutes twice a day for 24 weeks. The primary endpoint is the refraction change. The secondary endpoint is the axial length change. Statistical analysis was performed at a significant level of 0.05, using a two-tailed test. The criterion for significantly improved refraction was −0.17 ± 0.50 D/6 months and that of axial length change was 0.126 mm.

Results and Conclusions

This study did not include a control group because children represent a vulnerable group. This objective study will bring some impact on Korean medical myopia treatment. A long-term confirmatory clinical study may be necessary in future.

Key words : Myopia, Periocular, Acupoint stimulation, Acupressure, Medical device

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Ⅰ. Introduction

Most myopia is 'school myopia'. Myopia has a higher prevalence rate of 50 ~ 80% in Korea, Taiwan, Japan, which have higher educational fever, than that of 20 ~ 50% in USA and Europe[1]. Recently, the prevalence rate of myopia has been increasing and according to the Korea National Health & Nutrition Examination Survey in 2008, it was reported that 58% of the population older than 5 years old and 80.4% of the population between 12 and 18 years old develop myopia[2]. For this reason, there are many cases that refer to this condition as 'school myopia' or 'growth-induced myopia'.

Considering that the prevalence rate is higher in the East, it is predictable that social costs paid for myopia on Korean people will increase rapidly. Therefore, this study was sought to prevent and treat progressing myopia and exclude unnecessary treatment so that increases in medical expenses can be curbed.

It is expected that the prevalence rate will continue to increase consistently. There are many efforts to develop methods for preventing the progress of myopia: medications (pirenzepine, tropicamide, atropine, and so on), contact lenses, and special glasses (overcorrection glasses, bifocal glasses, progressive multifocal glasses)[3]. However, a medication treatment for effectively controlling the progress of myopia has not yet been developed. Actually, most vision correction is based on glasses or contact lenses. The only methods for changing the refractive poweron angle and shortening the optic axis are surgeries, such as keratotomy. However, surgery can be performed in adults only if the progression of the refractive error has stopped; these procedures can cause complications such as irregular astigmatism, glare at night, central islands, corneal opacity, etc.

Although the need for development of ing myopia treatments is urgently neededincreasingly urgent, studies are lacking. There have been several previous overseas studies on the therapeutic effect of acupressure of acupoints for myopia. Li reported that the improvement rate of visual acuity was 92.24% in 1216 myopia patients[4]. Liu reported that treatment effective in 98.5% of 424 patients[5]. Cheng and Chu reported that the treatment was effective in 88.5% of 629 patients[6]. Based on these studies, it seems that the acupressure therapy is effective for myopia. Those corresponding studies only evaluated a simple improvement in visual acuity and the subjective symptoms of the patient, but did not evaluate the change in refraction power that can be objectively examined. Thus, they are limited for evaluating the effect of myopia treatment.

We set up the objective evaluation variables for refractive error. By measuring any changes in myopia progression over 24 weeks, this study is an exploratory clinical trial aimed at suggesting a traditional Korean Medical therapy for myopia treatment.

Ⅱ. Materials and Methods

1. Study period

This study begins from the approved date of the clinical trial plan by the Korean Food and Drug Administration (KFDA) until December 31st, 2016.

2. Study objective

This is a pilot study that is aimed at evaluating the ability of acupressure therapy to the periocular acupoints to produce a temporary mitigating effect on the progression of myopia.

3. Study design

This study is an investigator-sponsored, prospective, and superiority pre & post single-armed study. We will use a medical massager for to produce the acupressure in the myopia subjects. After use, we will prospectively analyze whether acupressure on the periocular acupoints effectively mitigates myopia progression based on the comparison of the measurement of the refraction status and the axial length to before and after the intervention.

We will conduct this trial as an open-label trial that is not double blind regarding the investigators and subjects. The efficacy endpoints will be measured by objective indicators so that it may reduce the possibility of

bias from the investigator or subject, which is possible in an open-label clinical trial.

4. Medical device

This trial uses a medical massager (Nurieye-1, Seodong Medical Co. South Korea) that exerts vibrations around eyes. The periocular acupoints such as BL-01 (睛明), ST-01 (承泣), BL-02 (攢竹), GB-37 (光明), KI-05 (水泉), 'Y-mng (翳明)', 'Xi-jngmng (下睛明)', GB-16 (目窓), and others are mainly used as the main therapeutic acupoints for myopia treatment. The massager consists of 22 acupressure rods that only touch the margin of the eyes when they are closed. The action mechanism is as follows: when the vibration begins in the touched area, the massager stimulates the area automatically. The massager consists of an exterior case, a control panel, an operating part for the vibration setting, stimulating rods made of soft silicon and jade tip (only touches around the eyes when they are closed), and an adaptor. Fig. 1 is the image of device.

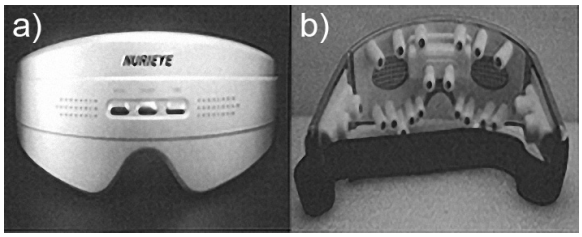

Fig. 1. Medical massager used in this study.
a): an anterior view, b): a posterior view

5. Recruitment

1) Number of subjects and calculation basis

(1) Proposed number of subjects

Based on two-tailed hypothesis testing the mean comparison of a group, we set up the difference as 0.21 between the refraction change of the known historical control group from baseline to the 24th week (-0.38) and that of the experimental group over the same period (-0.17). The total number of subjects is 45 to obtain a power of 80% at a standard deviation (SD) of 0.5 and a significance level of 0.05. Considering a drop-out rate of 20%, at least a total of 56 subjects will be registered.

The number of subjects (n) is calculated as follows:

[Hypothesis]

H0: δ=0.21 vs H1: $\delta \neq 0.21$

(δ: mean difference between the general patients and the experimental group)

$$n = \left(\frac{(z_{\alpha/2} + z_{\beta}) \cdot \sigma}{\delta} \right)^2$$

Significance level (α): 0.05

Type Ⅱ error (β): 0.2

Power of test (1-β): 0.80

Predicted difference of means (δ): 0.21

SD (σ): 0.50

Drop-out rate: 0.2 (=20%)

(2) The basis of calculation

No studies that measure refraction changes as an objective endpoint of using acupuncture or acupressure treatment have been reported. Therefore, we were not able to propose studies based on the number of subjects. Thus, based on discussion with a collaborator and an ophthalmologist, we decided to set up the change in the refraction power as the primary endpoint to precisely measure the visual acuity because it is clinically used as an objective endpoint. Because there is no previous study that reported the refraction change in response to acupuncture or acupressure, we calculated the number of subjects on the basis of research results using an orthokeratologic lens that has recently been clinically tested and is often used clinically.

The natural myopia progression in pediatric patients who were diagnosed with myopia and whose spherical equivalent was less than -5 D was −0.38 ± 0.42 D/6 months in Kim's study[7]. It was −0.17 ± 0.50 D/6 months in response to wearing orthokeratologic lens so the mean difference between two groups was 0.21. The degree of natural myopia progression was 0.67 ± 0.37 D/12 months in Doo's study[8], -0.25 ± 0.31 D/12 months after wearing orthokeratologic lens for 1 year compared to the beforerestult in Lee's study[9], and 0.25 ± 0.43 D/12 months in Choi's study[1]. Doo's result converted to D/6 months is -0.335 D; in Lee's and Choi's studies, this was 0.125 D. Consequently, the difference between the two groups was 0.21 D and it was determined that this was not different from Kim's result. Therefore, the mean difference in the

refraction change between subjects who used a medical massager for acupressure to the periocular acupoints and the untreated observed group was calculated as 0.21 based on Kim's result.

2) Inclusion and esxclusion criteria

(1) Inclusion criteria

- Children between 7~12 years old
- Spherical equivalent less than -5 D and a school myopia diagnosis
- No strabismus noted by covered tests at near and far gaze
- No anisometropia (difference in the spherical equivalent is within 1.0 D in both eyes)
- Determined participation and voluntarily signed written consent or with the guardian's intention

(2) Exclusion criteria

- Glaucoma, cataract, retinal detachment or other severe eye diseases
- Injury to the eye area or head area
- History of an operation in the eyes with a surgical site that has not yet healed
- A high fever or difficulty with wearing or operating the device alone
- Current use of a bifocal lens or a history of bifocal lens use
- A systemic or neurological problem that affects vision development
- Long-term medication that affect visual acuity or myopia progression

6. Intervention

Participants will undergo an acupressure treatment on the periocular acupoints by a medical massager. The device for the clinical trial is the Nurieye-1 medical massager (Fig. 2). Participants will use the Nurieye-1 for 15 minutes twice a day for 24 weeks. After use, we will evaluate clinical results.

7. Study procedure

Fig. 3 is a flow chart of the study procedure. The clinical trial researchers will explain any inconvenience and instructions during the subjects' first visit. The subjects who consented will be selected based on screening tests of visual acuity, refraction inspection, slit lamp examination, intraocular pressure (IOP) measurement, fundoscopy, axial length measurement, and interview. The subjects should complete the informed consent. All tests performed on the first visit will be conducted, and adverse events will be checked on every visit. During the progress observation period, the investigators should assess the compliance of the subjects and identify any adverse events. The observation and clinical checkups will be performed as shown in Table 1.

1) Subject screening

(1) Baseline characteristics of the subjects

Prior to starting this clinical trial, the investigator should check each subject's baseline characteristics and medical history in an interview and record them on the case report form. The baseline characteristics include demographic information (name, age, height, weight, gender, and contact information), vital signs (blood pressure and

Fig. 2. How to wear Nurieye-1

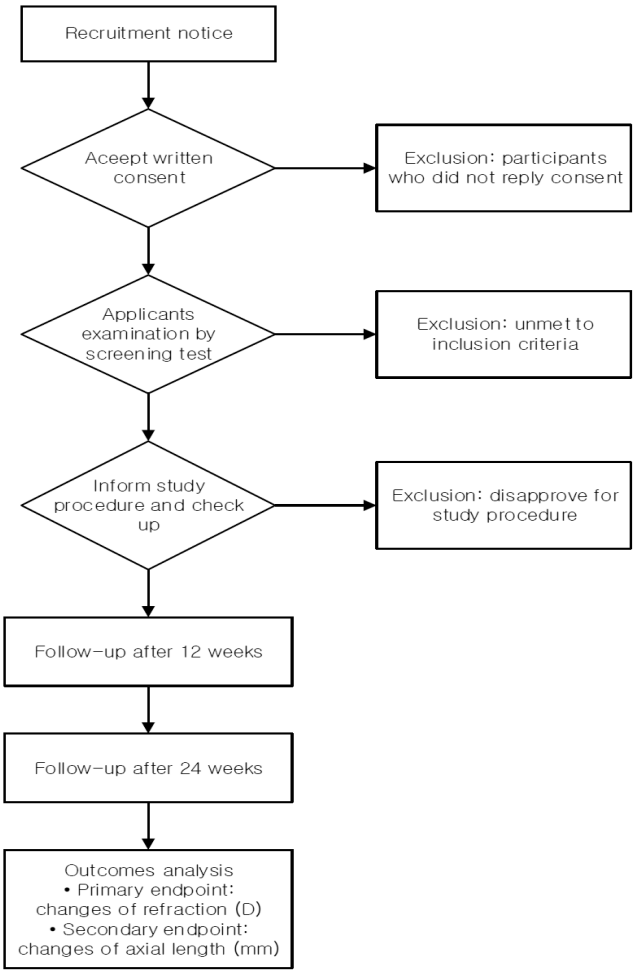

Fig. 3. Flow chart of the study procedure

Table 1. Observation and Checkup Plan

Observation and Checkup List		Screening	12th week	24th week
Visit		1st	2nd	3rd
Baseline character of subjects		○		
Written consent		○		
Medical history investigation		○		
Inclusion criteria		○		
Exclusion criteria		○		
Confirming exclusion criteria		○	○	○
Distributing medical massager for clinical trial		○		
Tests	Visual acuity test	○	○	○
	Slit lamp examination	○	○	○
	Refraction inspection	○	○	○
	IOP · fundus examination	○	○	○
	Axial length measurement	○	○	○
Adverse events assessment		○	○	○
Compliance assessment		○	○	○
Others[a]		○	○	○

pulse rate), wearing glasses or lenses, near-working hours (amount of reading and computer use), and posture at work. Studies involving children should investigate all potential risks including factors that are not generally considered in studies in adults; that information includes the effect of growth[10]. The investigator then performs a thorough medical history so that he/she screens subjects for the inclusion criteria.

(2) Identification code assignment to subjects

Agreed subjects will be screened by baseline character investigation, medical history investigation, interview, and so on. Furthermore, they should meet the inclusion and exclusion criteria. The subject identification code will be given to suitable subjects.

2) Clinical tests

Among collaborators, a pediatric ophthalmologist with more than 3 years of experience conducts the checkups: visual acuity test, slit lamp examination, refraction inspection, IOP measurement, and fundus examination. Tests will be performed by the same experienced examiner at every visit. To minimize the subjects' behavior changes that affect myopia, all subjects will be enrolled in this study without knowing their initial spherical equivalent.

(1) Visual acuity test

In the case of children, the visual acuity test is a clinically useful test to evaluate the development of normal visual acuity and diagnose diseases such as amblyopia in their early stages. We will use the Han Chun-suk visual acuity chart, which is widely used, and this test relatively easily detects the degree of myopia within 3 minutes[11,12].

(2) Refraction inspection

This study will use cycloplegic refraction among various refraction assessment tests. It is difficult to assess the exact refraction because children have very strong accommodation forces so sometimes they appear as myopia even if the child has hyperopia. To prevent this, cycloplegic refraction removes accommodation by using mydriatics, and assesses refraction. Thus, it is an essential test for assessing refraction in children[13]. Investigators will have the children take the test in a comfortable atmosphere after relaxing for 10 minutes in the examination room. Investigators will also allow them to go home after relaxing for 10 minutes after the test. A full auto ref-keratometer (RK-F1 Full Auto Ref-keratometer, Canon Components, Inc., Japan) will be used for the cycloplegic refraction. The required test time is 20 minutes, and the test will be conducted 1 hour after the mydriatics application of tropicamide/phenylephrine hydrochloride (Miydrin-P ophthalmic solution, Santen Pharmaceutical Co., Ltd., Japan) eye drops[14]. The mydriatics will be instilled 3 times at 5-minute intervals[14]. We will test the paralysis of accommodation with a penlight; we will make sure that there is no movement of the pupil and the pupil is dilated enough[15].

(3) Slit lamp examination

Slit lamp examination checks the abnormality of the cornea and lens by using a slit lamp microscope (Slit Lamp BQ-900, Haag-Streit AG, Switzerland). With this test, whether the subjects meet the exclusion criteria and whether the adverse events occurred can be checked. The required test time is 2 minutes.

(4) IOP fundus examination

According to a study on the correlation between intraocular pressure and myopia, the average IOP of the myopia group was significantly higher than that of the non-myopia group in children[16]. Thus, IOP examination is also an appropriate assessment method. A full auto tonometer (Canon Full Auto Tonometer TX-F, Canon Components, Inc., Japan) will be used and the required test time is 2 minutes.

Fundus examination observes the intraocular structures; it helps to diagnose abnormalities of the retina, choroid, and optic nerve. By conducting fundoscopy at each visit, we can identify other ocular diseases so that we can determine the adverse events and whether a subject can continue the trial or be an included/excluded target. Non-mydriatic retinal camera (TRC-NW200, Topcon Corporation, Tokyo, Japan) will be used and the required test time is 2 minutes.

(5) Axial length measurement

Physiologically, myopia is related to refraction of the eye and the axial length of the eye; especially, the axial length, which greatly contributes to myopia. Several studies reported that myopia progress is associated with the increase of in axial length[17,18]. Axial length will be measured by IOL Master (IOL Master, Carl Zeiss, Dublin, CA, USA). It prevents the interference of the examiner's bias by based on skiascopy when the refraction inspection is only conducted. Consequently, it is the test that can identify the exact progression of myopia. The required test time is 2 minutes.

3) Compliance assessment

During the trial, compliance assessment will also be performed. When wearing the massager, the subject (or his/her guardian) should check the wearing time. The subject/guardian should take photos daily while wearing the massager and save them to a mobile phone. To increase the compliance, investigators should contact the subjects or their guardians and check the progress.

8. Outcomes

1) Performance evaluation criteria

(1) Endpoints

- Primary endpoint: the refraction change from baseline to the 24th week
- Secondary endpoint: the change of the axialin length from baseline to the 24th week
- Safety endpoint: vital signs, height, weight, results of the slit lamp test, IOP measurement, and fundus examination

(2) Primary endpoint evaluation

The primary endpoint of this study is the refraction change from baseline to the 24th week. Refraction is presented by the diopter unit (D). Whether the refraction change follows a normal distribution will be tested. Depending on whether it is a normal distribution, the refraction change will be tested using one sample t-test or one sample Wilcoxon's signed-rank test. Descriptive statistics (mean, SD, minimum, and maximum) will be expressed as measured data at each point.

If refraction is significantly improved after the use of the massager compared to the baseline data before use, this finding will demonstrate that the medical massager has a valid clinical effect by suppressing myopia progression. The criterion of significantly improved refraction was set at -0.17 ± 0.50 D/6 months[6], and myopia is considered 'improved' if the refraction change does not exceed -0.17.

(3) Secondary endpoint evaluation

The secondary endpoint of this study is axial length change. Axial length measures the value before and after use of the massager, and descriptive statistics (same items as 4.1) are expressed as measured values at each point. Based on Chen[19], the change in axial length in the historical control group over 6 months was calculated at 0.228 mm. In the literature review, the axial length changes for 6 months in the experimental group were as follows according to Watanabe[20], Choi[1], and Cheng[21]: 0.235 mm when using accommodative training device, 0.06 mm when using atropine eye drop, 0.155 mm in super vision lens treatment, and 0.102 mm when using bifocal glasses. Thus, this study will set the criterion of significantly improved axial length change in the 24th week as 0.126 mm, which is the mean of these values. If the axial length change follows a normal distribution, it will be analyzed using one sample t-test; if not, one sample Wilcoxon's signed-rank test will be tested.

(4) Safety endpoint

The main analysis target of the safety evaluation analysis is the safety set. Vital signs and anthropometry results (height and weight) are expressed as the mean, SD, minimum, and maximum. Paired t-test will be used to check whether there is a difference between changes between before and after the trial.

Adverse event identification and safety evaluation will be performed by slit lamp test, IOP measurement, and fundus examination that checks for eye diseases through observing the cornea or lens. Regarding adverse events that occurred throughout this clinical trial, the number of subjects experienced adverse events once or more as

well as the percentage will be calculated. The number of subjects, the severity of adverse events, their relation to the use of the medical device and the percentage will be calculated.

2) Safety assessment

(1) Vital Signs and Anthropometric Results (height and weight)

Considering the age group of our subjects in the period of growth and development, anthropometric results and vital signs such as height and weight can be factors that affect myopia onset and progression. Therefore, it is necessary to measure them at the screening stage and during subsequent visits. Furthermore, abnormalities in vital signs and anthropometric data are identified as adverse events and are recorded in the safety assessment as soon as they reported.

(2) Adverse events

The specifics and the frequency of side effects and adverse events in all subjects in this study will be recorded on the case report form. They will be classified by whether they are related to the medical massager. Safety will be assessed based on these events.

3) Measurement point

This study is a prospective follow-up study with a limit of 2 follow-up visits. Thus, baseline data will be measured by tests before the clinical trial starts, and the results data will be measured after 12 and 24 weeks. Measured data in each test will be compared as follows: baseline-after 12 weeks, baseline-after 24 weeks, and after 12 weeks-after 24 weeks.

4) Measurement method

Children in this clinical trial will undergo screening tests to determine baseline data, and a population that meets the inclusion criteria will be selected. Then, the subject and his/her guardian will visit the center to receive instructions on the medical massager, warnings, and specific requirements for this study; it will be ensured that they are well-informed after the explanation. After the visit, the trial will be performed at each subject's home. If they require help for the study procedure and inconvenience, they can receive assistance through a telephone consultation with the person responsible for this study or visit.

9. Statistical analysis

1) Study population included in the analysis

(1) Full analysis set (FA set)

The main analysis target of significance evaluation is FA set. FA set is as follows; the analysis target group that 'intention-to-treat (ITT)' can be applied to most closely and completely is FA set; ITT means including all subject groups that meet the selection criteria based on the screening tests at the first visit. Generally, ITT shows less therapeutic effect than per protocol (PP) analysis so that it can prevent overestimation of the therapeutic effect; therefore, ITT analysis is recommended in the superiority trial. Thus, the target is all subjects enrolled in this trial who used the medical massager. However, the subject who is considered that he/she seriously violated the study proposal as follows will be excluded from the analysis:

- At the time of screening, he/she could not enroll because he/she failed to meet the inclusion/exclusion criteria.
- The data after using the massager is not available.

(2) PP protocol

In FA set, the following cases are considered serious violations of the study proposal, and relevant subjects will be excluded:

- Taken prohibited concurrent medications or use of a concurrent medical device
- Subjects with less than 80% compliance
- Other situations that can be considered severe study proposal violations

(3) Missing value handling

If missing values occur or subjects dropped out before finishing the clinical trial, the most recently collected data will be analyzed if the data were collected at a relevant point (Last Observation Carried Forward; LOCF).

According to the LOCF method, the cases that in which missing values are replaced will be as follows, but the method of replacing the missing values for the last observation value is limited to whether the compliance of the subject is over 80% (if not, the subject will be excluded from the analysis):

- It is excluded from analysis if missing values occurred in all of the data from the 12^{th} and 24^{th} weeks.
- Data from the 12^{th} week exists but a missing value occurred in the 24^{th} week, replace the 24^{th} week data with the 12^{th} week data.

2) Safety set

At the first visit, all subjects will wear the medical massager for 15 minutes identical with the designed procedure to identify whether there are abnormal symptoms. The investigators should check for discomfort and adverse events and record them in the safety assessment. Within 1 week of using the massager, investigators should determine safety by checking for unanticipated abnormal symptoms that occurred after a lapse of time using a call or in-person visit. Even if investigators do not involve the subjects who exhibit adverse events in this study, the results of adverse events will be included in the safety assessment result.

3) Baseline & outcome comparability

Statistical analysis of this clinical trial will be conducted by using SPSS statistical program (version 21.0, SPSS Inc., Chicago, IL, USA). We will analyze the primary endpoint and the secondary endpoint as follows; if the endpoints follow a normal distribution, we will use one sample t-test; otherwise, one sample Wilcoxon signed rank test will be used. All statistical tests will be performed based on a significance level of 0.05, a two-tailed test and 95% confidence intervals.

10. Adverse events

1) Anticipated side effects and caution for use

There are no assumable adverse events because the massager has been registered as a 'medical appliance', and the safety of the medical massager used in this clinical trial has been proved. If there are allergic reactions or tissue damage from adverse events with the massager, subjects will be prohibited from using it and should obtain adequate care from clinical-testing practitioners.

Anticipated side effects are as follows: sudden decrease in visual acuity, continuing eye pain, sudden floater in the of eyes (vitreous floaters), visual field deficits, signs (redness, swelling, or peeling) of skin contacting the device, dizziness or nausea before or after use

2) Adverse events

'Adverse event' denotes a little abnormal change in the subject's health or a side effect occurring in a subject. Adverse events can be categorized into serious/minor, anticipated/unanticipated, and study-related/unrelated event. 'Adverse device event (ADE)' denotes an adverse event associated with the medical massager.

3) Serious adverse event

'Serious adverse event' is the case corresponding to one of the followings among adverse events occurring with the medical device used in this clinical trial: death or risk of death, requires hospitalization or extension of hospitalization, causes continuous/meaningful disability or dysfunction, causes congenital malformation or disorder.

11. Ethics

We prepared this study based on the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Pusan National University Korean Medicine Hospital (PNUKH), Yangsan, South Korea (approval No.: 2013022). Furthermore, this study was enrolled in the Clinical Research Information Service (CRIS) (http://cris.nih.go.kr, CRIS Registration Number: KCT0001248) and ClinicalTrials.gov (http://www.clinicaltrials. gov,ClinicalTrials.gov Identifier: NCT02064660).

Ⅲ. Discussion

In Korea, the prevalence of myopia has gradually increased because of high educational fever and rapid in-

crease in computer use. Therefore, for myopia caused by cyclospasm from excessive near work, relieving it to restore visual acuity or preventing it its progression is important. This study aims to evaluate the effect of periocular acupressure therapy using a medical massager for myopia prevention or for mitigating myopia progression.

This study does not include a control group. Generally, setting a control group increases internal validity so it increases the reliability of the study. However, setting a control group can be skipped based on several studies. First, according to An's final report, a control group is necessary if the primary endpoint is based on subjective observation data, but the control group can be skipped if the primary endpoint is measured objectively without biases[22]. In this study, the refraction change is the primary endpoint and is an objective endpoint that is measured in diopter units using a refractometer without subjective intervention. Second, according to the 'Assessment Guidelines of Clinical Studies in Children' of the KFDA[10], children represent a vulnerable group that special factors are necessary for protecting their rights. For this reason, investigators should pay attention to subject agreement and should make efforts to minimize the risks and stresses. Moreover, investigators should also strive to reduce the number of subjects and procedure to limit the types and number of invasive methods for minimizing risks and fears and to use the safest methods with which the effect can be monitored. Based on these studies, we selected a single-armed design when considering that the target of this study is children because we determined that ethical problems occur from performing substantial treatments in children when setting up a control group. Instead, because several previous clinical trial results on mitigating myopia progression have been reported, we are going to report our result compared with the collected control group from these studies.

This study is based on acupressure, whose effects have been reported in some prior studies. Furthermore, we are going to suggest the Korean medical myopia treatment method, which has no established study yet, and the measurement of the refraction change, which is objective. Then, a long-term clinical trial that considers the evaluation of variables, the number of subjects, and the study period is necessary for mitigating myopia progression and treating myopia.

Ⅳ. Abbreviations

KFDA: Korean Food and Drug Administration; SD: Standard deviation; IOP: Intraocular pressure; FA set: Full analysis set; ITT: Intention-to-treat; PP: per protocol; LOCF: Last observation carried forward; ADE: Adverse device event; IRB: Institutional Review Board; PNUKH: Pusan National University Korean Medicine Hospital; CRIS: Clinical Research Information Service.

Ⅴ. Competing interests

The authors declare that they have no competing interests.

Ⅵ. Acknowledgements

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