

Acupuncture as Adjuvant Therapy for Glaucoma : Protocol for a Randomized Controlled Trial.

Yi-Fang Liao, Yu-Chen Lee, Hui-Ju Lin, Yi-Ching Shao

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Acupuncture as Adjuvant Therapy for Glaucoma : Protocol for a Randomized Controlled Trial.

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Abstract

Background: Introduction?Glaucoma is a chronic progressive optic neuropathy that necessitates lifelong treatment to retard the decline of the optic nerve. Due to the extended and continuous treatments required for patients, they may explore alternative or complementary therapies alongside conventional treatments to enhance the effectiveness in controlling disease progression. Acupuncture has displayed promise in the treatment of various ophthalmic disorders in clinical trials, and its potential to reduce intraocular pressure (IOP) makes it an intriguing candidate for managing glaucoma.

Objective: The primary objective of this trial is to conduct a single-center clinical trial involving glaucoma patients, wherein acupuncture will be evaluated as an adjunctive therapy, aiming to explore its effectiveness for glaucoma.

Methods: In this single-center, randomized, controlled trial, 50 patients diagnosed with primary open-angle glaucoma will be randomly allocated to two groups: the treatment group and the control group. Participants in the treatment group will undergo acupuncture targeting ophthalmology-related acupuncture points, aiming to elicit the 'De Qi' sensation. Conversely, the control group will receive minimum acupuncture stimulation targeting non-ophthalmic acupuncture points without the intention of achieving the 'De Qi' sensation. Both groups will undergo acupuncture therapy once a week for a total of six sessions and will be observed for twelve weeks. The primary outcome will be the variation in IOP before and after each acupuncture session. Secondary outcomes will encompass pre- and post-acupuncture measurements of heart rate and blood pressure. Additionally, assessments will be conducted for best-corrected visual acuity, visual field, optical coherence tomography (OCT), OCT-angiography, glaucoma symptom scale, and the glaucoma quality of life-15 questionnaire, with comparisons made against baseline measurements.

Results: Ethics approval was obtained from the institutional review board of China Medical University Hospital (CMUH111-REC3-210), and was registered on clinicaltrials.gov (NCT05753137). Recruitment of participants for the trial commenced on June 28, 2023, and currently, only a limited number of participants have been enrolled to test the feasibility of the experiment. We anticipate that the preliminary data from this trial will be completed by 2025.

Conclusions: This trial employs rigorous methodology and comprehensive outcome measurements to assess the clinical efficacy of acupuncture as an adjunctive therapy for glaucoma, providing valuable insights for future clinical treatment guidelines. Clinical Trial: ClinicalTrials.gov NCT05753137, registered on 2023/01/29

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Original Manuscript

Acupuncture as Adjuvant Therapy for Glaucoma - Protocol for a Randomized Controlled Trial

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Abstract

Introduction

Glaucoma is a chronic progressive optic neuropathy that necessitates lifelong treatment to retard the decline of the optic nerve. Due to the extended and continuous treatments required for patients, they may explore alternative or complementary therapies alongside conventional treatments to enhance the effectiveness in controlling disease progression. Acupuncture has displayed promise in the treatment of various ophthalmic disorders in clinical trials, and its potential to reduce intraocular pressure (IOP) makes it an intriguing candidate for managing glaucoma.

Objective

The primary objective of this trial is to conduct a single-center clinical trial involving glaucoma patients, wherein acupuncture will be evaluated as an adjunctive therapy, aiming to explore its effectiveness for glaucoma.

Methods and analysis

In this single-center, randomized, controlled trial, **50** patients diagnosed with primary open-angle glaucoma will be randomly allocated to two groups: the treatment group and the control group. Participants in the treatment group will undergo acupuncture targeting ophthalmology-related acupuncture points, aiming to elicit the 'De Qi' sensation. Conversely, the control group will receive minimum acupuncture stimulation targeting non-ophthalmic acupuncture points without the intention of achieving the 'De Qi' sensation. Both groups will undergo acupuncture therapy once a week for a total of six sessions and will be observed for twelve weeks. The primary outcome will be the variation in IOP before and after each acupuncture session. Secondary outcomes will encompass pre- and post-acupuncture measurements of heart rate and blood pressure. Additionally, assessments will be conducted for best-corrected visual acuity, visual field, optical coherence tomography (OCT), OCT-angiography, glaucoma symptom scale, and the glaucoma quality of life-15 questionnaire, with comparisons made against baseline measurements.

Results

Ethics approval was obtained from the institutional review board of China Medical University Hospital (CMUH111-REC3-210), and was registered on clinicaltrials.gov (NCT05753137). Recruitment of participants for the trial commenced on June 28, 2023, and currently, only a limited number of participants have been enrolled to test the feasibility of the experiment. We anticipate that the preliminary data from this trial will be completed by 2025.

Conclusions

This trial employs rigorous methodology and comprehensive outcome measurements to assess the clinical efficacy of acupuncture as an adjunctive therapy for glaucoma, providing valuable insights for future clinical treatment guidelines.

Trial registration number: ClinicalTrials.gov NCT05753137, registered on 2023/01/29

Keywords: acupuncture, open-angle glaucoma, optical coherence tomography, intraocular pressure

Background

Glaucoma is a chronic optic nerve disease involving progressive loss of retinal ganglion cells, necessitating long-term treatment with minimal side effects. Some patients may supplement their conventional medical interventions with complementary or alternative medicine.[1-3]

Acupuncture, a traditional Chinese medical therapy, has been widely used as an alternative treatment for ophthalmic conditions. Possible mechanisms of acupuncture treatment have been proposed, including the release of neurochemical substances through acupuncture stimulation, the influence of acupuncture on ocular blood flow parameters [4,5], and the upregulation of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) expression in the retina.[6] In the review of acupuncture treatment for glaucoma, Law et al conducted a prospective study involving 11 glaucoma patients and observed a short-term increase in intraocular pressure (IOP) after acupuncture.[7] However, another study presented a different perspective, suggesting that acupuncture at acupoints BL1 and EX-HN7 was beneficial in reducing IOP.[8] Systematic literature reviews have also supported the potential of acupuncture in lowering IOP and improving visual fields.[9] Long-term follow-up data is limited. On the other hand, comprehensive and detailed protocols help reduce bias in acupuncture outcomes for glaucoma and enhance the reproducibility of treatment.

Therefore, the primary objective of this trial is to conduct a single-center clinical trial involving glaucoma patients, wherein acupuncture will be evaluated as an adjunctive therapy. A total of 50 participants are expected to be enrolled, and the observation period will span twelve weeks. The objective is to evaluate the clinical efficacy of acupuncture in the context of glaucoma and provide a reference for future clinical treatment guidelines.

Methods

Design and setting

The trial is designed as a single-center randomized controlled, parallel-arm trial. It will take place in the clinic of China Medical University Hospital. The trial will be conducted from June 2023 until 50 patients finish acupuncture treatment and follow-up assessment. The trial was approved by the institutional review board of China Medical University Hospital (CMUH111-REC3-210), and was registered on clinicaltrials.gov (NCT05753137). This protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials checklist.[10]

The main purpose of the trial is to investigate the effectiveness of acupuncture in the treatment of glaucoma, including its potential to decrease IOP and reduce optic nerve damage. All participants will be randomly assigned to two groups: the treatment group and the control group. Participants in the treatment group will receive acupuncture treatment targeting acupuncture points related to ophthalmology, while participants in the control group will receive minimum acupuncture stimulation targeting nonophthalmic acupuncture points. Additionally, all participants will undergo ophthalmic examinations and follow-up. Figure 1 illustrates the enrollment process of the trial. The assessments will include measurements of IOP, heart rate (HR), blood pressure (BP), best-corrected visual acuity (BCVA), central corneal thickness, visual field (VF), optical

coherence tomography (OCT) imaging, OCT-angiography and visual function questionnaire.

Patient involvement

Patients were involved in the design and implementation of this study. We recruited a limited number of participants to assess the feasibility of the trial and evaluate the measures. Based on participant feedback, we made adjustments to the experimental design and recruitment strategies.

Participants

A total of 50 patients with open-angle glaucoma will be included in this trial, provided that they meet the trial inclusion criteria and their legal representatives sign the informed consent.

Inclusion criteria

- Primary open angle glaucoma diagnosed at least 3 months ago.
- Diagnosed with mild or moderate open angle glaucoma.
- Use 1 or 2 kinds of glaucoma drugs.
- Female or male.
- Age ≥ 20 years old.
- All participants will be required to sign an informed consent form and cooperate with the experimental procedures.

Exclusion criteria

- Accept any ophthalmic laser or surgery within one year.
- High myopia ($\leq -6.0D$).
- Use of any drugs that affect IOP.
- Visual acuity with correction lower than 0.2.
- Previous or existing uveitis or retinopathy.
- Unable to receive acupuncture treatment continuously or allergic to acupuncture needles.
- Pregnancy or breastfeeding.
- Refusal to sign the informed consent form.

Informed consent

The informed consent discussion will take place before the trial. The informed consent form will be explained in clear and understandable language by a hospital doctor, and it will cover the intervention, risks, benefits, and patient rights in the trial. The informed consent form will be signed by the patients or their legal guardian. In the event that a patient wishes to withdraw from the trial, we will use the available data for the final analysis and accommodate their wishes accordingly.

Randomization and allocation concealment

The participants will be randomly assigned to 2 groups with a 1:1 ratio using random number generation in Excel. A computer-based simple random sampling without stratification with a 1:1 ratio will be used. After the random allocation is completed, the researchers will assign sequential numbers (1-50) to the participants and prepare 50 folders. The appearance

of the folders will be identical for both groups, and the section containing the participant's group and the intervention measures will be sealed. When participants complete the informed consent process, the acupuncturist will unseal the section and begin the acupuncture treatment.

Blinding

Upon revealing the treatment allocation, the acupuncturist will proceed to administer acupuncture based on the patient's assigned group. Throughout the entire experiment, all sterile needles will have the same appearance, thickness, and size. Only the acupuncturist will be aware of the patient's group allocation.

Participants will be informed that there are two different acupuncture groups, but they will only receive one of them. Additionally, they will undergo treatment in separate rooms to prevent any communication between them. At the end of the trial, participants will be orally questioned about whether they are aware of the treatment strategy they received, confirming the effectiveness of the blinding implementation. Throughout the entire study, there will be no communication between the acupuncturist and the participants, as well as between the acupuncturist and the assessors. This is to maintain blinding of the participants, researchers, assessors, and statisticians to the group allocation.

Procedures /interventions

Patients who meet the inclusion criteria at the Ophthalmology Clinic of China Medical University Hospital in Taiwan will be enrolled in a trial and randomly assigned to different groups.

Both groups of patients will receive ophthalmic prescriptions and care. Acupuncture treatment will be performed using sterile acupuncture needles manufactured by "Jia Shun" (FDA: No. 000470).

After the acupuncturist unseals the section, they will disinfect the acupoints using alcohol pads containing 70% alcohol. Then, they will administer acupuncture treatment by inserting the needles perpendicularly into the muscle layer, followed by up and down manipulation to induce the "De Qi" sensation in the treatment group. However, the control group will not experience the "De Qi" sensation; the needles will penetrate the skin, but the needling process will be halted as soon as the patients start feeling stimulation. During the 20-minute acupuncture session, the patients will maintain a supine position or a sitting position. The acupuncturist is not allowed to communicate with the patients during the trial, except to inquire about the sensation of "De Qi". Additionally, after patients are enrolled in the trial, if no serious adverse events occur, the ophthalmologist evaluator will remain blinded and isolated until the completion of the trial at the 12th week to maintain the integrity of blinding in the trial.

Treatment group

In addition to routine ophthalmic prescription treatments, patients in the treatment group will receive weekly traditional Chinese medicine-style acupuncture at the following bilateral acupoints: Fengchi (GB20), Cuanzhu (BL2), Sibai (ST2), Taiyang (EX-HN5), Hegu (LI4), and Taichong (LR3), for a total of six acupoints. The acupoint selection in this group is specific to treat symptoms of glaucoma. Figure 2 shows Acupoints used in the treatment group.

Control group

In addition to routine ophthalmic prescription treatments, patients in the control group will receive weekly minimum acupuncture stimulation at the following bilateral acupoints: Yinlingquan(SP9), Liangqiu (ST34), Xiajuxu(ST39), Yanglingquan (GB34), Shousanli(LI10), Sanyangluo(TE8), for a total of six acupoints. Figure 3 shows acupoints used in the control group. The non-ophthalmological acupoints are not indicated for the treatment of ophthalmological related pathologies, and are not reported to improve ophthalmological function.

Outcome measures

The primary outcome is the change in IOP as measured using the TOPCON CT-80 Computerized Tonometer. Prior to the start of the trial, the participants' baseline IOP will be measured. Subsequently, IOP data will be collected before each acupuncture treatment and 15 minutes after the treatment. By comparing these measurements, the effect of acupuncture treatment on IOP can be assessed.

The secondary outcomes include the long-term effects of acupuncture on the eyes. Baseline measurements and measurements after the completion of the sixth acupuncture session will be taken using OCT-A [AngioVue®; QuickVue version] to assess the vessel density of the radial peripapillary capillary and macula. Additionally, VF, OCT, BCVA, central corneal thickness, and two questionnaires will be recorded at baseline and during follow-up at week 12. VF measurements will be conducted using the Humphrey Field Analyzer 3 from ZEISS to measure the mean deviation (MD), pattern standard deviation (PSD) and visual field index (VFI) values. OCT imaging will be performed using the ZEISS HD-OCT model 5000, and measurements of retinal nerve fiber layer (RNFL), ganglion cell complex and symmetry and cup-to-disc (C/D) ratio will be recorded. The two questionnaires used in the trial are the Glaucoma Symptom Scale scales (GSS)(0 to 100) and the Glaucoma Quality of Life-15 (GQL-15)(0 to 75).[11.12] These questionnaires are used to quantify the extent of functional impairment or inconvenience in patients with glaucoma. Additionally, to ensure the safety of participants during the trial and to address other relevant considerations related to the pathophysiology of glaucoma, BP and HR measurements will be taken at baseline, before and after acupuncture sessions, and during follow-up assessments. Figure 4 depicts the trial schedule, illustrating the journey of patients from initiation to the completion of the trial.

Adverse events

We will document the location of adverse reactions, the acupuncture site, the time of occurrence, the duration of symptoms, and the recovery status. Additionally, appropriate medical resources and financial assistance, such as arranging emergency or outpatient care, will be provided to participants as needed.

Statistical analysis

The statistical analysis will be performed by a researcher who is completely blind to patient allocation, using SPSS software version 29.0 (SPSS Inc, Chicago, IL). The demographic data between the two groups, including sex, age, initial IOP, HR and BP, BCVA will be compared using Student's t-test. For the data from the two glaucoma questionnaires, a one-way analysis of variance (ANOVA) will be used based on previous similar studies. Additionally, a repeated measures analysis will be conducted in the trial. The data will be presented as mean \pm standard deviation, and a P-value of less than 0.05 will be

considered statistically significant. Subgroup analysis will be conducted based on factors such as age, gender, changes in IOP before and after treatment, VF, OCT and OCTA data, central corneal thickness, among others. In cases of small sample size, the Mann-Whitney U test and the Wilcoxon signed-rank test will be implemented accordingly. Missing data will be analyzed using pairwise deletion.

Dissemination

When we complete the trial, we will submit it to a peer-reviewed journal for publication.

Discussion

Glaucoma, the second leading cause of blindness globally, necessitates continuous exploration of alternative or complementary therapies to enhance conventional treatment efficacy. This study delves into the potential of acupuncture as an adjunctive therapy for glaucoma, drawing inspiration from compelling evidence from previous research. The selection of acupuncture points was based on the following arguments. Shin Takayama et al. conducted acupuncture on 11 patients with open-angle glaucoma, targeting the following acupoints: BL2, M-HN9, ST2, ST36, SP6, KI3, LR3, GB20, BL18, and BL23. This treatment showed a significant reduction in IOP and had effects on the short posterior ciliary artery (SPCA) and improvement of retrobulbar circulation.[4] The ophthalmic artery is responsible for the main blood supply to the eyes, while the anterior cerebral artery, middle cerebral artery, and ophthalmic artery are downstream branches of the internal carotid artery. In a series of studies, it has been observed that the acupoints GV20, GB20, and GB34 are associated with increased blood flow velocity in the anterior cerebral artery and middle cerebral artery, as well as increased cerebral blood flow (CBF).[13-15] In a mouse model of traumatic optic neuropathy (ONC), the acupoint GB20 significantly altered the expression of post-traumatic retinal genes. This suggests that acupuncture may target specific genes involved in the treatment of glaucoma, such as Mt3 (associated with ocular neovascularization) and Fbn1 (related to macular degeneration).[16]

LR3 is an acupoint located on the liver meridian. It is known for its functions related to “soothing the liver,” “regulating blood,” and “affecting the eyes.” According to traditional Chinese medicine theory, LI4 and LR3 are considered as intermediate stations for the gathering and transformation of energy within the body. The combination of acupuncture stimulation at these two acupoints is referred to as “the four gates.” It is commonly used to promote the circulation of Qi and blood throughout the body and can influence brain areas involved in blood pressure regulation, thus having a regulatory effect on blood pressure.[17,18] LR3 activation leads to the activation of the visual cortex BA 19 and the inhibition of the ipsilateral BA 17 and 18 .[19,20] Additionally, LR3 also results in a significant reduction in vascular resistance in the central retinal artery (CRA) and SPCA.[21] Patients with migraine have an increased risk of developing open-angle glaucoma (OAG) and the most commonly used acupoints in acupuncture for this condition are EX-HN5 and GB20.[22-24] LI4 is also believed to be associated with pain relief, particularly in the treatment of muscle or nerve pain or paralysis in the head and face, and has shown significant benefits. [25]

Acupuncture can produce multiple effects on the body, including the regulation of intraocular pressure, promotion of local and systemic blood circulation, protection of the optic nerve, and relief of glaucoma symptoms. Based on these beneficial effects, we

chose the acupoint combination of EX-HN5, GB20, BL2, ST2, LI4, and LR3 for treatment.

The effectiveness of glaucoma treatment extends beyond clinical measures and should consider the holistic well-being of individuals. Therefore, this study assessed the influence of acupuncture on the daily life convenience and functionality of individuals with glaucoma, utilizing the Glaucoma Symptom Scale (GSS) and the Glaucoma Quality of Life-15 (GQL-15) questionnaire. This includes evaluating the psychological, social, and functional dimensions that contribute to their overall well-being. By extending the focus to these elements, we gain a more understanding of the treatment's effects on the individuals' day-to-day experiences and functionality.

This study strengthens our understanding of acupuncture as a potential adjunctive therapy for glaucoma. Methodological rigor, including a randomized controlled study, enhances the credibility of findings. The comprehensive evaluation, incorporating diverse outcome measures such as IOP, cardiovascular parameters and various ophthalmic assessments, provides valuable insights into acupuncture's impact on glaucoma management. The twelve-week observation period contributes valuable information on both short-term and potential long-term effects. However, limitations include the single-center design, affecting generalizability, and a modest sample size that may compromise statistical power. The study's duration may not fully capture long-term effects. Concerns about publication bias highlight the importance of transparent reporting.

Study Status

Recruitment of participants for the trial commenced on June 28, 2023, and currently, only a limited number of participants have been enrolled to test the feasibility of the experiment. We anticipate that the preliminary data from this trial will be completed by 2025.

Figure 1. The figure illustrates the enrollment process of the trial.

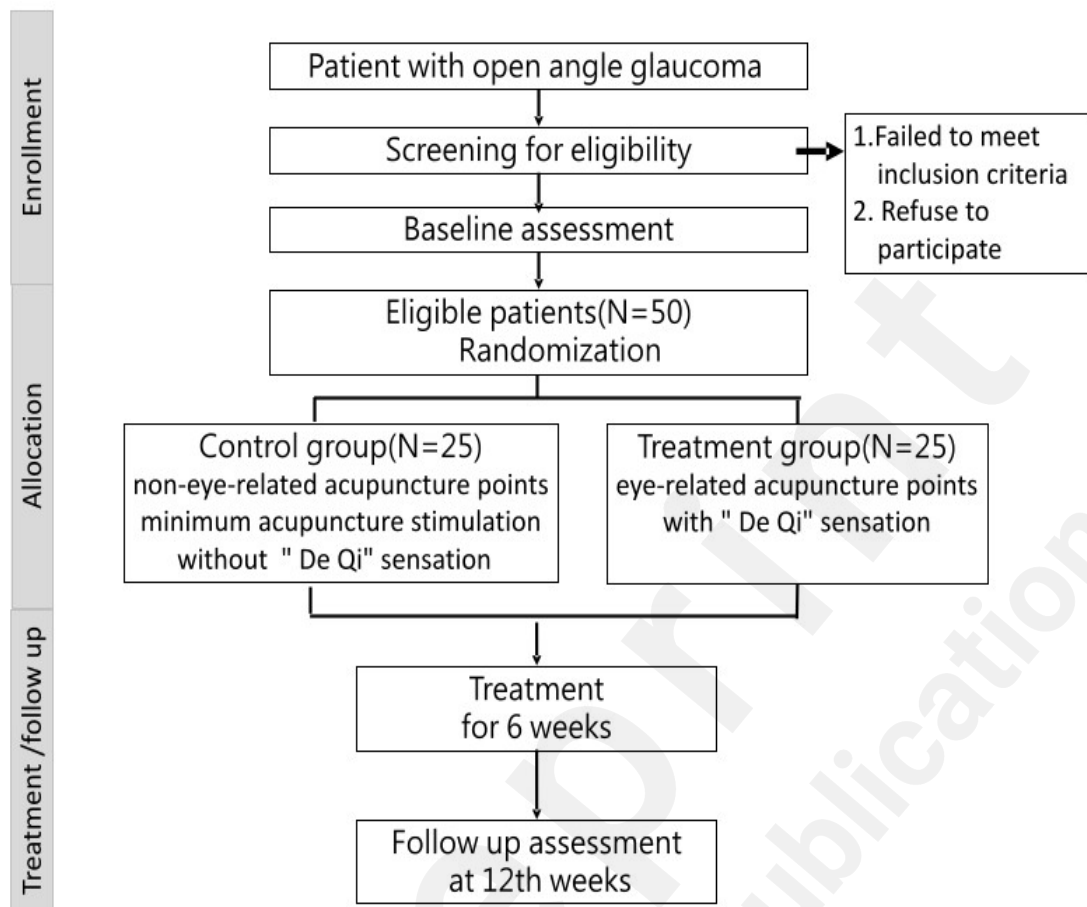


Figure 2. Acupoints used in the treatment group: Fengchi (GB20), Cuanzhu (BL2), Sibai (ST2), Taiyang (EX-HN5), Hegu (LI4), and Taichong (LR3).



Figure 3. Acupoints used in the control group: Yinlingquan(SP9), Liangqiu (ST34), Xiajuxu(ST39), Yanglingquan (GB34), Shousanli(LI10),and Sanyangluo(TE8).

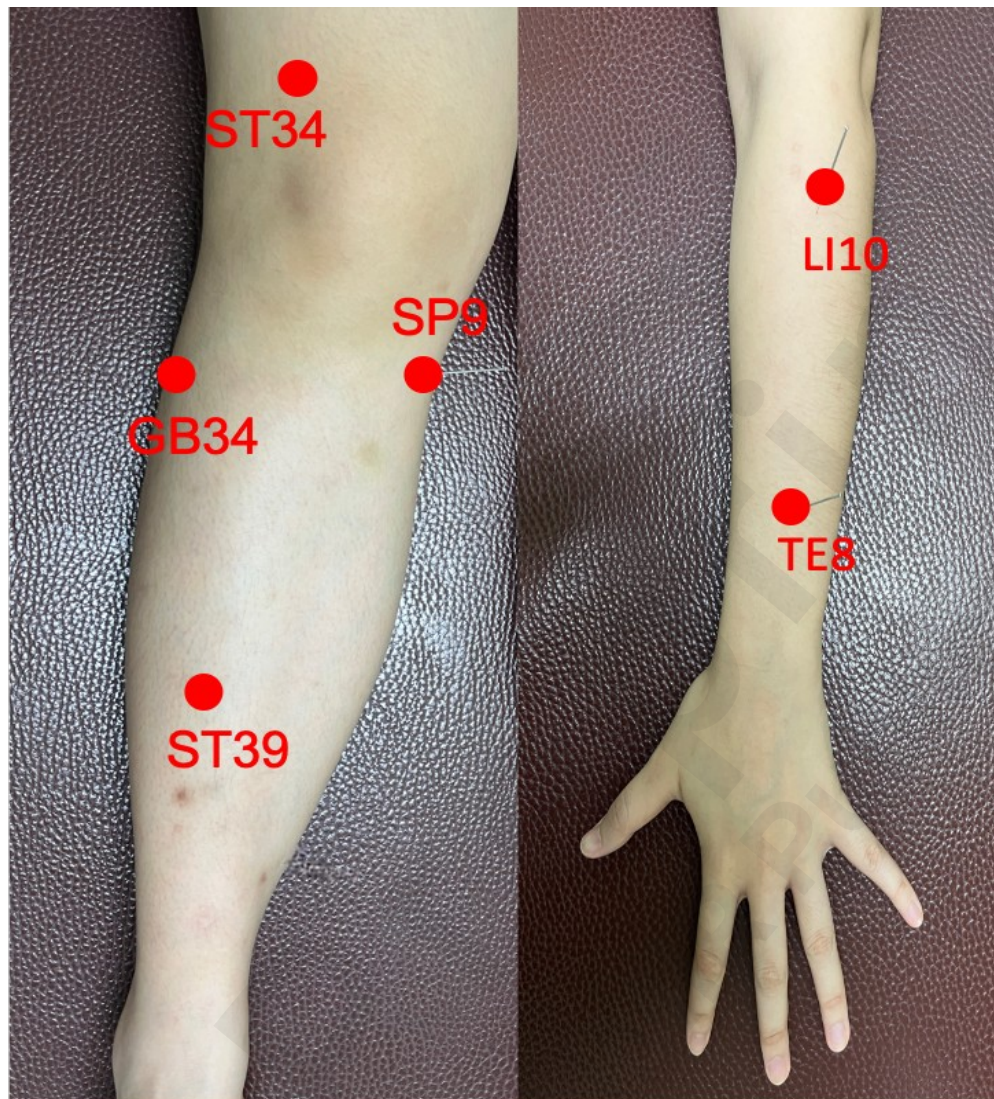


Figure 4. The figure depicts the trial schedule, illustrating the journey of patients from initiation to the completion of the trial.

	Enrollment	Treatment		Follow up
Timepoint:	Visit day 1	Week1 ~week6	Week6(after- acupuncture)	Week 12
Eligibility screen	0			
Informed consent	0			
Allocation	0			
Acupuncture				
Treatment group		0		
Control group		0		
Data collection				
Intraocular pressure				
Blood pressure				
Heart rate				
OCT-A	0		0	
OCT	0			0
BCVA	0			0
visual field	0			0
Central corneal thickness	0			0
GSS	0			0
GQL-15	0			0
Abbreviations: Best-corrected visual acuity (BCVA); Optical Coherence Tomography (OCT); Optical Coherence Tomography angiography (OCTA); Glaucoma Symptom Scale (GSS); Glaucoma Quality of Life-15 (GQL-15)				

Acknowledgments

We appreciate the personnel at the Ophthalmology Department of China Medical University Medical Center for their knowledge and professional technical support. The investigators would like to express their sincere appreciation for the valuable contributions of the participants.

Author contribution

YF and SYC conducted data analysis and interpretation. YF conceptualized the study. YF performed formal analysis. Funding acquisition was managed by LYC. Both YF and SYC were involved in the investigation, and YF, SYC, LYC, and HJ contributed to the methodology. Project administration was handled by LYC and HJL, and they were responsible for the allocation of resources. LYC also oversaw the supervision. YF took charge of data curation, formal analysis, and software usage. Validation was conducted by SYC and LYC.

Abbreviations:

Intraocular pressure (IOP);

Best-corrected visual acuity (BCVA);

Visual field (VF);

Optical Coherence Tomography (OCT);

Optical Coherence Tomography angiography (OCTA);

Blood pressure (BP);

Heart rate (HR);

Glaucoma Symptom Scale (GSS);

Glaucoma Quality of Life-15 (GQL-15).

Funding: This research is funded by China Medical University, with the project number CMU111-IP-02.

Data

Availability:

The trial contains original contributions, which can be found in the article. For any additional

inquiries, please contact the corresponding author directly.

Declarations:

Ethics approval and consent to participate

This protocol was approved by the ethics committee of the China Medical University Hospital (No. CMUH111-REC3-210) and registered in ClinicalTrials.gov (No. NCT05753137). All participants will sign written informed consent.

Consent for publication

Not applicable.

Competing interests

There is no competing interests regarding the publication of this protocol.

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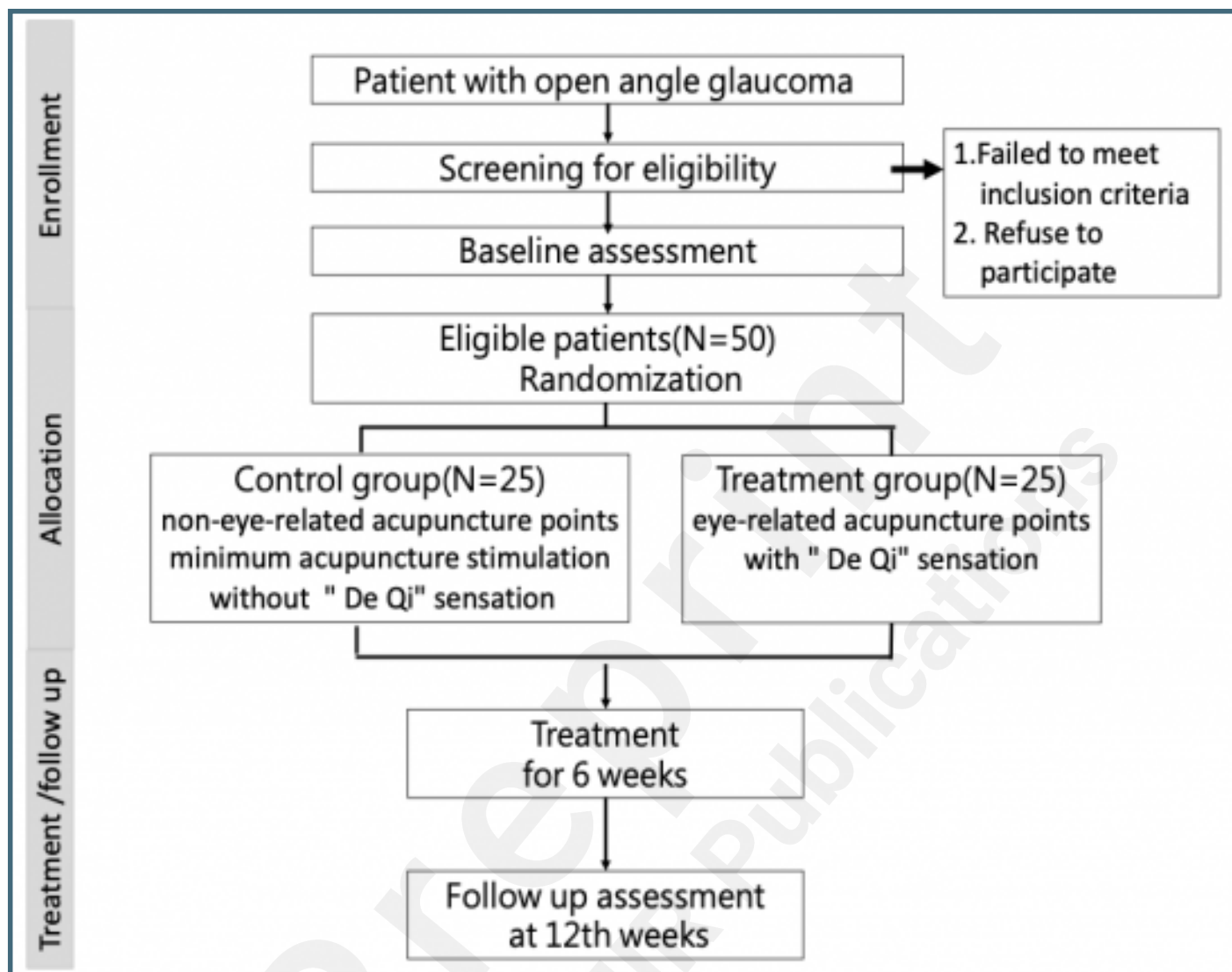
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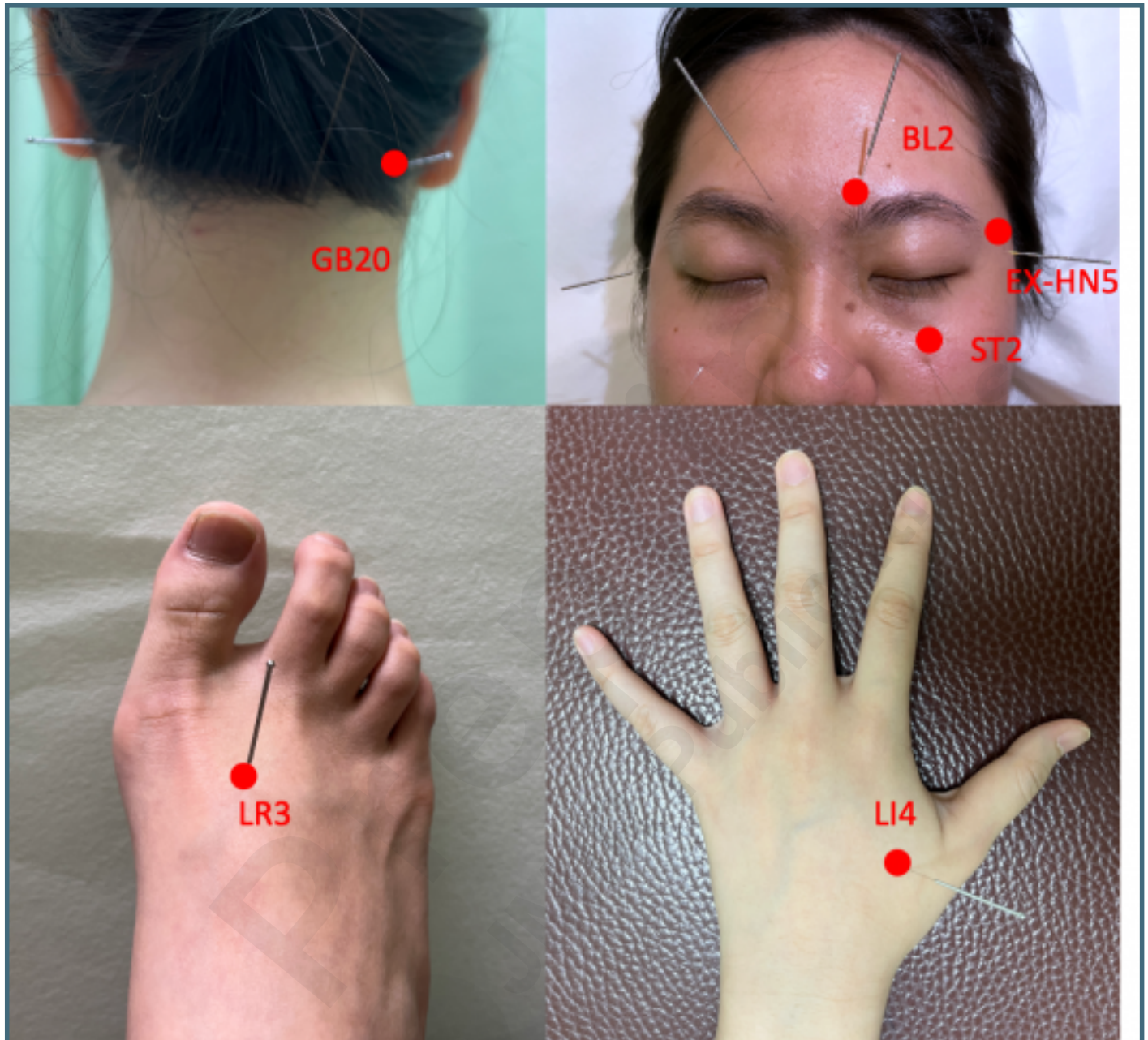
Supplementary Files

Figures

The figure illustrates the enrollment process of the trial.






Acupoints used in the treatment group: Fengchi (GB20), Cuanzhu (BL2), Sibai (ST2), Taiyang (EX-HN5), Hegu (LI4), and Taichong (LR3).



Acupoints used in the control group: Yinlingquan(SP9), Liangqiu (ST34), Xiajuxu(ST39), Yanglingquan (GB34), Shousanli(LI10),and Sanyangluo(TE8).



The figure depicts the trial schedule, illustrating the journey of patients from initiation to the completion of the trial.

	Enrollment	Treatment		Follow up
Timepoint:	Visit day 1	Week1 ~week6	Week6(after- acupuncture)	Week 12
Eligibility screen	0			
Informed consent	0			
Allocation	0			
Acupuncture				
Treatment group		0		
Control group		0		
Data collection				
Intraocular pressure				
Blood pressure				
Heart rate				
OCT-A	0		0	
OCT	0			0
BCVA	0			0
visual field	0			0
Central corneal thickness	0			0
GSS	0			0
GQL-15	0			0
Abbreviations: Best-corrected visual acuity (BCVA); Optical Coherence Tomography (OCT); Optical Coherence Tomography angiography (OCTA); Glaucoma Symptom Scale (GSS); Glaucoma Quality of Life-15 (GQL-15)				

CONSORT (or other) checklists

This protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials checklist.
URL: <http://asset.jmir.pub/assets/a636c351bc6168b6bb4420e45f1cca7c.pdf>

