BMJ Open

Electroacupuncture for mild-to-moderate dry eye: study protocol for a multicentre, randomised, single-blind, sham-controlled trial

Yun-Qiong Lu ,[1] Guang Yang,[2] Mei-Yan Li,[3] Jue Hong,[2] Yan-Ting Yang,[2] Xue-Jun Wang,[3] Xie-He Kong ,[2,4] Yue Zhao,[2] Zhao Ma,[1] Xin-Yun Huang,[1] Yue-Lan Zou,[5] Xing-Tao Zhou,[3] Xiao-Peng Ma[1,2]

To cite: Lu Y-Q, Yang G, Li M-Y, *et al*. Electroacupuncture for mild-to-moderate dry eye: study protocol for a multicentre, randomised, single-blind, sham-controlled trial. *BMJ Open* 2023;**13**:e069369. doi:10.1136/bmjopen-2022-069369

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069369).

Received 28 October 2022
Accepted 25 October 2023

For numbered affiliations see end of article.

Correspondence to
Professor Xiao-Peng Ma; pengpengma@163.com, Yue-Lan Zou; yuelan123000@sina.com and Dr Xing-Tao Zhou; xingtaozhou@163.com

ABSTRACT

Introduction Dry eye (DE) is a multifactorial ocular surface disease causing considerable medical, social and financial implications. Currently, there is no recognised long-term, effective treatment to alleviate DE. Clinical evidence shows that electroacupuncture (EA) can improve DE symptoms, tear secretion and tear film stability, but it remains controversial whether it is just a placebo effect. We aim to provide solid clinical evidence for the EA treatment of DE.

Methods and analysis This is a multicentre, randomised, sham-controlled trial. A total of 168 patients with DE will be enrolled and randomly assigned to EA or sham EA groups to receive 4-week consecutive treatments and follow-up for 24 weeks. The primary outcome is the change in the non-invasive tear break-up time (NIBUT) from baseline to week 4. The secondary outcomes include tear meniscus height, the Schirmer I test, corneal and conjunctival sensation, the ocular surface disease index, corneal fluorescein staining, the numerical rating scale and the Chinese DE-related quality of life scale.

Ethics and dissemination The trial protocol and informed consent were approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine (identifier: 2021–119), Shanghai Eye Disease Prevention and Treatment Center (identifier: 2022SQ003) and Eye and ENT Hospital of Fudan University (identifier: 2022014).

Trial registration number NCT05552820.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first multicentre, randomised, sham-controlled trial evaluating the efficacy of electroacupuncture (EA) for dry eye.
⇒ The sham EA method is performed using non-penetration acupuncture and non-acupuncture points without electrical stimulation to blind the subjects and maximally circumvent therapeutic and non-specific effects.
⇒ The acupuncturists are not blinded due to the particularity of the EA intervention modality.

INTRODUCTION

Dry eye (DE) is a multifactorial ocular surface disease pathologically characterised by tear film instability, elevated tear osmolarity, ocular surface inflammation and injury and neurosensory abnormalities. DE has become a common health concern worldwide in recent years, with its global prevalence estimated as 5%–50%.[1] In China, the prevalence is 6.1%–59.1%, higher than the global average and increasing yearly.[2] A UK cross-sectional web-based survey showed that as DE symptoms worsened, patients were more affected in terms of social-emotional functioning, vision-related quality of life, daily activities and productivity.[3] Therefore, interventions in the early stages of DE are crucial to delay its progression and reducing social and economic stress.[4]

There is no gold standard for the treatment of DE yet. In clinical practice, first-line treatment usually focuses on adequately relieving DE symptoms, routinely with tear supplementation with ocular surface lubricants.[5] However, their effects can be relatively transient, partly because reflux tearing and drainage via the nasolacrimal duct clear ≥80% of the instilled drug very quickly after application.[6] Besides, the long-term daily use and the high cost of eye drops hinder patients' treatment adherence and efficacy. Therefore, it is necessary to find a treatment method that treats DE and is also characterised by high safety, good compliance, tolerance and cost-efficiency.

Acupuncture has been widely used as a complementary and alternative therapy. Substantial clinical evidence shows that acupuncture can improve DE symptoms, tear secretion and tear film stability with more

significant efficacy than artificial tears.[7–10] Its long-term effects are also satisfactory.[11] The mechanism of acupuncture for treating DE has not yet been fully elucidated. However, existing studies have shown that its action is multitargeted, including improving structural and functional abnormalities of the ocular surface, regulating apoptosis and autophagy of ocular surface cells, inhibiting immune-inflammatory responses and promoting neurotransmitter secretion.[12] In addition, recent experimental studies have demonstrated the potential of electroacupuncture (EA) as a critical modulator of immune-inflammatory reactions by inhibiting the reactive oxygen species/thioredoxin-interacting protein/NOD-like receptor pyrin domain containing-3 signalling cascade or the modulation of the alpha 7 nicotinic acetylcholine receptor/nuclear factor-kappa B signalling pathway.[13 14] Currently, it remains controversial whether it is just a placebo effect.[15 16] Our preliminary study found that, compared with 0.1% sodium hyaluronate eye drops, EA exerted more beneficial and long-lasting effects after 4 weeks of treatment.[17] To rule out the placebo effect of EA, we propose conducting a multicentre, randomised, subject-blind and sham EA-controlled trial to provide high-quality clinical evidence to support using EA to treat DE.

METHODS AND DESIGN

Trial design and setting

This will be a 28-week multicentre, randomised, subject-blind, sham-controlled trial carried out at three clinical centres, including Shanghai Research Institute of Acupuncture and Meridian, Shanghai Eye Disease Prevention and Treatment Centre and Eye and ENT Hospital of Fudan University. The trial flow chart is illustrated in figure 1, and the schedule of treatment assessments and data collection is shown in table 1. The trial will be conducted according to the Standard Protocol Items: Recommendations for Intervention Trials guidelines[18] (Additional file 1) and adhere to the principles of the Consolidated Standards of Reporting Trials[19] and the Standards for Reporting Interventions in Clinical Trial of Acupuncture.[20] The trial protocol and informed consent were approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine (identifier: 2021–119), Shanghai Eye Disease Prevention and Treatment Center (identifier: 2022SQ003) and Eye and ENT Hospital of Fudan University (identifier: 2022014) and registered with ClinicalTrials.gov (identifier: NCT05552820).

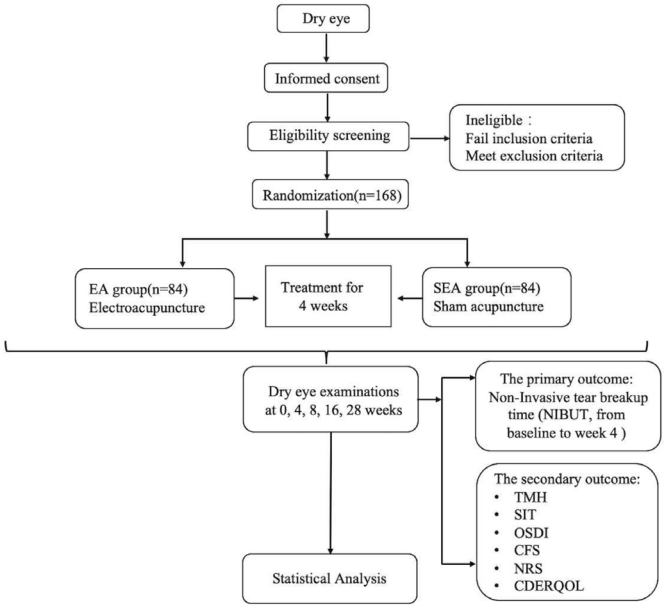

Figure 1 Flow diagram of the trial procedure.

Subjects

We will post on official social media and posters in hospitals and communities. People with intentions can contact the researchers by telephone or in person. We will inform the subjects of the study protocol and obtain written informed consent before screening them according to the inclusion and exclusion criteria. The included subjects will be randomly allocated at 1:1 to receive 4-week EA or sham EA treatments. We will then conduct a 24-week follow-up for further observation. All procedures will rigorously adhere to the Declaration of Helsinki.

Eligibility

Inclusion criteria

1. Patients meeting the diagnostic criteria for mild-to-moderate DE according to the Tear Film and Ocular Surface Society Dry Eye Workshop II[21]: Ocular surface disease index (OSDI) ≥ 13, < 33 and NIBUT <10 s.
2. Age 18–65 years, no gender limit.

Exclusion criteria

1. Combined with other eye diseases (eg, severe blepharitis, blepharospasm, conjunctival laxity, strabismus, amblyopia, glaucoma, cataract, fundus disease and ocular trauma).
2. With active eye diseases or a history of eye surgery within 3 months.
3. Received acupuncture treatment or other DE treatment within 1 month that may influence the assessment of efficacy.
4. Previously experienced EA intervention.
5. Pregnant or breastfeeding women.
6. With serious systemic diseases such as cardiovascular, cerebrovascular, hepatic, renal and haematopoietic system and psychiatric disorders.
7. With autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus or ankylosing spondylitis.
8. With damaged, ulcerated, infected or scarred skin at the selected acupuncture points.
9. Allergic to metal or tape.

Table 1 Schedule of treatment assessments and data collection

		Study period					
	Enrollment and baseline	Allocation	Postallocation				Close-out
Time point (week)	–	0	4	8	16	28	
Informed consent	×						
Inclusion/exclusion	×						
General information	×						
Random allocation		×					
Intervention (EA or sham EA)		×	×				
Concomitant medication	×		×	×	×	×	×
NIBUT	×		×	×	×	×	
TMH	×		×	×	×	×	
Corneal and conjunctival sensation	×		×	×	×	×	
CFS	×		×	×	×	×	
SIT	×		×	×	×	×	
OSDI	×		×	×	×	×	
NRS	×		×	×	×	×	
CDERQOL	×		×	×	×	×	
PHQ-9	×		×	×	×	×	
GAD-7	×		×	×	×	×	
IVCM	×		×				
Adverse events and other unintended effects			×	×	×	×	
Blind evaluation			×				
Compliance			×	×	×	×	×
Completion summary							×

CDERQOL, Chinese dry eye-related quality of life scale; CFS, corneal fluorescein staining; EA, electroacupuncture; GAD-7, generalised anxiety disorder; IVCM, in vivo confocal microscopy; NIBUT, non-invasive tear break-up time; NRS, numerical rating scale; OSDI, ocular surface disease index; PHQ-9, patient health questionnaire-9; SIT, Schirmer I test; TMH, tear meniscus height.

Randomisation and blinding

Eligible subjects will be randomly assigned to either the EA group or the sham EA group evenly via a central randomisation system. A randomisation sequence will be produced by third-party personnel not involved in the trial using SAS V.9.4. Permuted blocks with block sizes of 2 and 4 and centre-stratified randomisation are implemented to ensure allocation concealment. Numbered, sealed, opaque envelopes will be delivered to the research assistant at each centre. Subjects, examiners, data collectors and statisticians are unaware of the grouping, but only acupuncturists can access it. Researchers will only break the mask to take action in case a serious adverse event happens. After the first and last treatment sessions, subjects' blindness to treatment modalities will be validated by the Treatment Credibility Scale, where they will be asked whether the treatment is logical, whether it is considered successful and how confident it can help patients with DE.[22 23] If the subjects of both groups hold equal expectations of efficacy, the potential psychological placebo effect produced by EA can be ruled out; if not equal, this means that the difference in results between groups is not solely due to the specific therapeutic effect of EA, and then the results should be interpreted with caution.

Intervention

In a previous study, we developed a standardised DE treatment protocol based on traditional Chinese medicine theory.[24] At each centre, one certified acupuncturist with over 3 years of clinical experience will be in charge of the treatment. DE treatments other than artificial tears are not permitted. Those who use artificial tears regularly before enrollment will continue their original medication regimen; those who do not use artificial tears before recruitment will remain off the regimen during the treatment and follow-up. The researcher will keep a complete record of the duration and dosage of the use of artificial tears. Each subject will receive treatment in a separate space, with medical tape to help close their eyes. They will also be asked to keep quiet to avoid communication and speculating about treatment assignments.

Table 2 Location of the acupoints

Point	Location
BL2	On the head, in the depression at the medial end of the eyebrow.
TE23	On the head, in the depression at the lateral end of the eyebrow.
EX-HN5	In the temporal region, between the tip of the eyebrow and the outer canthus of the eye, in a depression about one cross finger backward.
ST2	On the face, in the infraorbital foramen.
GV20	On the head, 5 Cun superior to the anterior hairline, on the anterior median line.
GB20	In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of sternocleidomastoid and the trapezius muscles.
LI4	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone.
ST36	On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 Cun inferior to ST35.
GB37	On the fibular aspect of the leg, anterior to the fibula, 5 Cun proximal to the prominence of the lateral malleolus.
SP6	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 Cun superior to the prominence of the media malleolus.
LR3	On the dorsum of the foot, between the first and second metatarsal bones, in the depression distal to the junction of the bases of the two bones, over the dorsalis pedis artery.

BL2, Cuanzhu ; EX-HN5, Taiyang; GB20, Fengchi; GB37, Guangming; GV20, Baihui; LI4, Hegu; LR3, Taichong; SP6, Sanyinjiao; ST2, Sibai; ST36, Zusanli; TE23, Sizhukong.

Electroacupuncture

In this study, Cuanzhu (BL2), Taiyang (EX-HN5), Sibai (ST2), Sizhukong (TE23), Baihui (GV20), Fengchi (GB20), Hegu (LI4), Zusanli (ST36), Guangming (GB37), Sanyinjiao (SP6) and Taichong (LR3) are used. All points are taken bilaterally, except GV20. The points are positioned according to the WHO Standard Acupuncture Point Locations in the Western Pacific Region[25] (table 2, figure 2).

To receive the treatment, patients are supine with their eyes closed. After routine disinfection of the points, a sterile polyethylene cylindrical needle pad will be put on each point. Sterile acupuncture needles (0.25 mm×0.40 mm, Hwato brand, Suzhou Medical Supplies Factory Co., China) are inserted into the points through the needle pads. The acupuncturist will then perform twisting and lifting operations at the points until the subject reports Deqi (acupuncture sensations such as soreness, numbness, distension and heaviness). The needle handles of each side of BL2 and EX-HN5 will attach to a pair of electrodes from an EA apparatus (SDZ-III type, Hwato brand, Suzhou Medical Supplies Factory Co., China) to receive electrical stimulation with a continuous wave at 2 Hz and a current of 1–2 mA. Each treatment session lasts for 30 min. The subjects will receive the treatment three times a week for four consecutive weeks (a total of 12 sessions), with at least 1 day off between treatments. The EA procedure follows a standardised method of operation.[26]

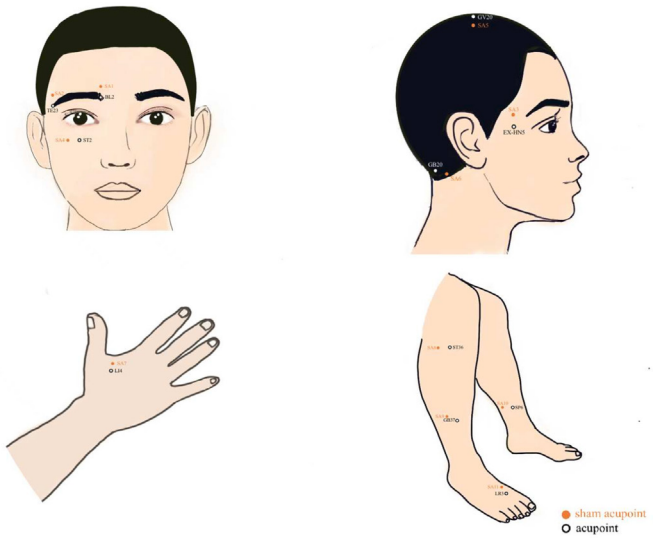

Figure 2 Acupuncture point diagram.

Sham EA

Sham points are used for sham EA here, selected near the points used in the EA group but away from meridians (table 3, figure 2). We chose Streitberger sham acupuncture needles (Asia-med GmbH, Germany) for the procedure, producing some tingling sensations when fixing the needles on the skin to convince the subject of needle insertion. However, the needle does not penetrate the skin but is only pressed against the skin and withdraws back.[27] The needles are kept upright by foam needle pads at the sham points, with the same appearance as the EA settings. Sham points SA1 and SA3 are connected to electrodes from the EA apparatus. The acupuncturist will turn on the machine to give the same external display and beeps and set the same parameters as in the EA group but disconnect the internal wires to disrupt electrical stimulation. The sham EA intervention's duration, frequency and number of sessions are the same as in the EA group.

Subjects who attend at least 10 sessions are considered to have completed the whole course of treatment.

Table 3 Location of the sham points

Sham point	Location
SA1	1 cm straight up from the midpoint of the line between BL2 and GB14.
SA2	1 cm superior to TE23.
SA3	1 cm superior to EX-HN5.
SA4	1 cm horizontally lateral to ST2.
SA5	Midpoint of the line between GV20 and Right EX-HN1.
SA6	Midpoint of the line between GB20 and TE16.
SA7	1 cm horizontally to the radial side of LI4.
SA8	Midpoint of the line between ST36 and GB34.
SA9	Midpoint of the line between GB37 and BL58.
SA10	Midpoint of the line between SP6 and EX-LE8.
SA11	Midpoint of the line between LR3 and SP4.

Assessments and outcomes

Subjects will be assessed at baseline and at weeks 4, 8, 16 and 28. Both eyes will receive DE measurements. The primary outcome measure is the NIBUT change from baseline to week 4. The secondary outcomes include tear meniscus height (TMH), Schirmer I test (SIT), corneal and conjunctival sensation, OSDI (0 (best)–100 (worst)), corneal fluorescein staining (CFS) (0 (best)–5 (worst)), ocular pain assessed by the numerical rating scale (NRS) (0 (best)–10 (worst)) and Chinese DE-related quality of life scale (CDERQOL) (five domains containing 45 items rated on a five-point Likert scale ranging from 1 (completely disagree) to 5 (completely agree)).[28 29]

The researcher will perform the objective ocular tests in the sequence of increasing invasiveness to minimise interferences.[30] The order will be NIBUT, TMH, CFS, corneal perception, conjunctival perception, SIT and NRS for ocular pain. First, the tear film rupture video is taken using MODI2 (CSO, Italy).[31] The subject is seated with the lower jaw on the jaw rest and the forehead firmly attached to the frontal band to fix the head. The subject will then be asked to blink naturally 3–4 times and keep looking at the central light source of the Placido disc until the examiner observes the breaking and deformation of the Placido rings, which is recorded as NIBUT. The measurement repeats three times, and the average value will be taken. After the NIBUT measurement, a digital slit lamp (SL990N, CSO, Italy) is applied to take images of the lower tear meniscus in a dark room. The system's built-in calliper measures the TMH directly below the pupil's centre.[29] Next, the CFS is performed to observe corneal epithelial integrity. The Cochet-Bonnet perception metre (Luneau Chartres, France) is used to evaluate the corneal perception (including central, superior, inferior, nasal and temporal corneas, all 2 mm from the corneal rim) and conjunctival perception (including temporal and nasal bulbar conjunctivae, both 3 mm from the corneal rim; superior and inferior conjunctivae, at the centre of the eyelid). The measured fibre lengths will be converted into pressure (g/mm^2) using a specifically calibrated curve, with a higher threshold indicating a more insensitive perception.[32] Then, tear secretion will be measured using SIT. The intensity of ocular pain will be evaluated using the NRS once before and 30 s after using 0.4% oxybuprocaine hydrochloride eye drops (Santen Pharmaceutical Co., Japan).[33] This scale is usually used to assess pain intensity with numbers ranging from 0 to 10; the higher the number, the greater the pain. In recent years, there has been an increasing interest in the relationship between DE and mental health.[34] Therefore, we will additionally apply the patient health questionnaire-9 (0 (no)–27 (severe))[35] and the generalised anxiety disorder (0 (no)–21 (severe))[36] to understand the mental health status of patients before and after treatment.[37]

Neurosensory abnormalities are one of DE's core pathological mechanisms.[38] Corneal nerves have an essential role in the tear secretion reflex and the maintenance of ocular surface health.[39] Corneal nerve fibres are shorter in length and less dense in patients with DE than in normal subjects,[40–42] and corneal nerve morphology is closely related to DE symptoms and visual quality.[43 44] Therefore, at baseline and week 4, we will perform in vivo confocal microscopy (IVCM) to take a primary look at the morphological changes of corneal subbasal nerves. IVCM is a non-invasive technique that examines the morphology of corneal subbasal nerves at the microstructural level. An experienced examiner will perform this test using the Heidelberg Retina Tomograph III (Heidelberg Engineering, Germany).[45] Before the examination, the ocular surface of each eye is anaesthetised with 0.4% oxybuprocaine hydrochloride eye drops. The focus is located at the corneal subbasal nerve plexus layer, with the sequence mode selected to scan 6–8 different spots of the cornea. A masked observer will pick up three clear and typical images of the corneal subbasal nerve. The ACC Metrics analysis software (M.A. Dabbah, Imaging Science Biomedical Engineering, Manchester, UK) is used to calculate the neuromorphological parameters of the selected images, namely corneal nerve fibre density, corneal nerve branch density, corneal nerve fibre length and corneal nerve fibre width. The average values are taken for statistical analyses.[41]

Adverse events

Any adverse events will be recorded. EA-related adverse events include local bleeding, subcutaneous hematoma, pain, itch, infection and generalised symptoms such as dizziness and palpitation during the treatment.

Data monitoring and management

All subjects' data will be managed using printed case report forms with double entry and validation by the EpiData 4.6 password-protected database. All investigators will receive training on data management. Paper and electronic data will all be kept for at least 3 years after

publication. In addition, an independent Data Safety Monitoring Committee (DSMC) consisting of three experts with backgrounds in ophthalmology, acupuncture and statistics will be established prior to the trial. The DSMC will hold an online conference every 4 months to oversee the trial progress and review the safety and quality of the data. At the stage of 1/2 enrollment, an interim analysis will be conducted, and the DSMC will decide whether it is necessary to terminate the trial in advance. Information involving personal privacy (eg, name, age, telephone number) will be concealed within DSMC reports.

Sample size

In the previous sham-controlled study,[46] the tear break-up time (BUT) increased from 3.29±1.01 s to 4.24±1.26 s in the acupuncture group versus 3.71±1.38 s to 4.00±1.34 s in the sham acupuncture group. Based on the formulas in the Cochrane Handbook[47] and the imputed correlation coefficient between the pretreatment and post-treatment values of BUT of 0.5,[16] the means and SD for changes in the BUT were calculated to be 0.95±1.16 s and 0.29±1.36 s in the acupuncture group and the sham acupuncture group, respectively. Thus, we estimated a sample size of 134 (67 subjects per group) to provide a power of 85% and a two-sided significance level of 5%. Assuming a 20% attrition rate, we increased the sample size to 168 (84 subjects per group).

Data analysis

An independent statistician will analyse the data using SAS software V.9.4 (SAS Institute). Analyses will be performed according to the intention-to-treat principle. The study will employ linear regression for continuous variables and the χ^2 test for categorical variables to compare subject-level characteristics at baseline and specific visits. Similarly, eye-level characteristics at baseline and typical visits will be compared using linear regression for continuous variables with generalised estimating equations to account for the correlation between eyes and logistic regression for categorical variables with generalised estimating equations.[48–50] Missing data for NIBUT will be addressed using propensity scores and multiple imputation regression methods. A mean change analysis of the NIBUT with adjustments for baseline values will be performed, followed by additional longitudinal data analyses to fully characterise the relation of the NIBUT change to the treatment group over time. A mixed-effects model with a random intercept for each subject will account for the correlation between repeated measurements. Time will be modelled as a categorical variable for a non-linear relationship between the NIBUT and time. An interaction term between time and treatment group will be included in the model and dropped if it is not statistically significant. These models will evaluate the correlation between the change in NIBUT from baseline to follow-up and the influence of possibly prognostic factors. All statistical tests are two-sided, and the statistical significance level will be 0.05.

Quality control

Before starting the trial, we developed an investigator's manual to standardise the assessment procedure, performance of EA and sham EA, DE measurements and data collection and entry. All the involved researchers will receive centralised and unified training to ensure strict adherence to the trial protocol and the standardisation and uniformity of the study. The true and sham EA interventions will be provided by licenced acupuncturists with at least 3 years of clinical experience. The acupuncturists at each site will be trained face-to-face by the senior acupuncturist from the lead site to standardise the intervention procedures, including greetings, preparations, the locations of points and sham points and the needling manipulations of both true and sham EA. Those who pass the quality assessment are qualified to take part in the trial.

DISCUSSION

This trial is designed to reveal the non-placebo and long-lasting efficacy of EA for mild-to-moderate DE and provide a feasible therapeutic strategy for treating DE. In addition, we will further investigate the association between EA's treatment efficacy and changes in the corneal nerve.

We have established a standardised EA procedure for DE treatment with high reproducibility.[24] The prescribed points include periocular and body points, known as the distal–proximal point combination. In light of the theory of traditional Chinese acupuncture, the distal–proximal point combination is a classic point prescription method widely used in the acupuncture treatment of DE, and it has been proven superior to selecting periocular points alone.[51] All the points on the head and face can be considered as proximal points near the eyes. Among them, BL2, TE23, EX-HN5 and ST2 are the most commonly used periocular points in treating DE.[51 52] At the local points, a mass of nerve endings and blood vessels are distributed in the hypodermis and muscles, interlacing with the collagen fibres.[53] Benefiting from this microanatomical structure, EA at BL2 and EX-HN5 can effectively stimulate the periocular nerves. In terms of body points, ST36, LI4 and LR3 are frequently prescribed for all sorts of diagnosis patterns based on network analysis.[53] The association rules analysis also shows that TE23 and LI4 can be used as the core point groups in treating DE.[52] The latest meta-analysis also suggested that 2–3 times of acupuncture per week for 21–30 days might be the most appropriate option for managing DE.[8] Thus, the EA intervention performed in this trial should be both theoretically and practically reasonable and beneficial.

In this trial, we employ a sham EA group as a control. Establishing an inert and concealable sham EA control is quite a challenge in acupuncture studies because of methodological difficulties.[54] In the previous DE studies,[11 15]

shallow needling at non-meridian non-acupuncture points was designed as a sham acupuncture control, whereas an unintended treatment effect on DE was still found, indicating that even superficial stimulation of sham acupuncture could lead to physiologic changes beyond a placebo effect.[55] We take the essence and make some adjustments to the published sham methods. So, the same number of non-meridian non-acupuncture points are used, located minimally 1 cm away from the standard acupuncture points. For needle insertion, non-skin-penetration sham acupuncture is performed, different from the penetration acupuncture adopted in the previous DE studies.[11 15] Some researchers reported that penetration acupuncture, even the shallow needling at non-acupuncture points, could induce a therapeutic effect,[56 57] which may explain the lack of a significant difference in some sham-controlled DE studies. Hence, the non-penetration sham method seems to be a better choice.[58 59] However, the controversy remains regarding whether a non-penetration sham acupuncture is physiologically inert on account that a slight mechanical stimulation with no skin penetration might evoke brain responses and physiological activities.[59 60] The sham EA control conducted here uses a device combining a blunt-tipped needle and a foam pad placed at the sham points. The needle will retract after touching the skin to give the patient the illusion that it has pierced the skin but actually has not. Besides, the foam pad helps to imitate the real acupuncture setting, increasing the patient's confidence in the treatment. In order to avoid electrical stimulation, the sham EA device is used with its internal electrodes disconnected. The exterior appearance, indicator light and prompt tone of the sham device are all indistinguishable from the normal one. To ensure concealment, subjects with real EA interventions will be excluded. Currently, this type of sham EA procedure is believed to be optimal enough to blind the subjects and maximally circumvent therapeutic and non-specific effects.[54]

Recruitment for this trial started on 12 October 2022 and is planned to be completed on 31 December 2023. The last follow-up assessment is planned to be finished in August 2024.

We should note several limitations in this protocol. First, the acupuncturists are not blinded due to the particularity of the EA intervention modality, but we will use standardised operations and avoid communication to reduce the influence. Second, the sham EA operation is not entirely inert. Nevertheless, the study is still deemed to provide high-quality evidence for the effectiveness of EA in treating DE and unveil the potential neuroregulatory mechanisms of EA.

ETHICS AND DISSEMINATION

The trial protocol (V.3.0, 11 November 2021) and informed consent were approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine (identifier: 2021–119), Shanghai Eye Disease Prevention and Treatment Center (identifier: 2022SQ003) and Eye and ENT Hospital of Fudan University (identifier: 2022014) and registered with ClinicalTrials.gov (identifier: NCT05552820).

Author affiliations
[1]Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[2]Shanghai Research Institute of Acupuncture and Meridian, Shanghai, China
[3]Eye and ENT Hospital of Fudan University, Shanghai, China
[4]Shanghai University of Traditional Chinese Medicine, Shanghai, China
[5]Shanghai Eye Disease Prevention and Treatment Center, Shanghai, China

Contributors LYQ, YG and LMY have contributed equally to this work and shared first authorship. Conception and design: ZXT, MXP, LYQ, YG and KXH. Administrative support: MZ and HXY. Provision of study materials or patients: ZYL and ZY. Collection and assembly of data: LYQ, YG, LMY and WXJ. Statistical method design: YG and KXH. Manuscript writing: LYQ, YG, HJ and YYT. All authors conceived or refined the trial design and approved the final manuscript.

Funding The study is supported by the National Science Foundation of China (81904302), the Scientific Research Project of Shanghai Municipal Health Commission (20214Y0116, 202040249, 201940130) and the Shanghai Sailing Programme (19YF1445000, 23YF1442000). The funding has no role in the design of the study, the collection, analysis and interpretation of data, or in writing the manuscript.

Competing interests None declared.

Patient and public involvement Patients were not involved in the design, conduct or reporting of this trial. They will be evaluated about the availability to complete study treatment based on their time and the degree of mobility difficulty.

Patient consent for publication Consent obtained directly from patient(s).

ORCID iDs
Yun-Qiong Lu http://orcid.org/0000-0002-0357-1840
Xie-He Kong http://orcid.org/0000-0002-8778-7445

REFERENCES

1 Craig JP, Nelson JD, Azar DT, *et al*. TFOS DEWS II report executive summary. *Ocul Surf* 2017;15:802–12.
2 Liu ZG, Wang H. Focusing on the management of chronic dry eye disease. *Chin J Ophthalmol* 2018;54:81–3.
3 Hossain P, Siffel C, Joseph C, *et al*. Patient-reported burden of dry eye disease in the UK: a cross-sectional web-based survey. *BMJ Open* 2021;11:e039209.
4 Yang W, Luo Y, Wu S, *et al*. Estimated annual economic burden of dry eye disease based on a multi-center analysis in China: a retrospective study. *Front Med (Lausanne)* 2021;8:771352.
5 Tong L, Petznick A, Lee S, *et al*. Choice of artificial tear formulation for patients with dry eye: where do we start? *Cornea* 2012;31 Suppl 1:S32–6.
6 Robert P-Y, Cochener B, Amrane M, *et al*. Efficacy and safety of a cationic emulsion in the treatment of moderate to severe dry eye disease: a randomized controlled study. *Eur J Ophthalmol* 2016;26:546–55.
7 Kim BH, Kim MH, Kang SH, *et al*. Optimizing acupuncture treatment for dry eye syndrome: a systematic review. *BMC Complement Altern Med* 2018;18:145.
8 Na J-H, Jung J-H, Park J-G, *et al*. Therapeutic effects of acupuncture in typical dry eye: a systematic review and meta-analysis. *Acta Ophthalmol* 2021;99:489–98.
9 Yang L, Yang Z, Yu H, *et al*. Acupuncture therapy is more effective than artificial tears for dry eye syndrome: evidence based on a meta-analysis. *Evid Based Complement Alternat Med* 2015;2015:143858.

10 Liu XX, Zhang D, Yang YT, *et al*. Efficacy observation of acupuncture for dry eye syndromes and its effects on patients' quality of life and anxious and depressed moods. *Shanghai J Acu-Mox* 2021;40:744–50.
11 Shin M-S, Kim J-I, Lee MS, *et al*. Acupuncture for treating dry eye: a randomized placebo-controlled trial. *Acta Ophthalmol* 2010;88:e328–33.
12 Yang G, Li XY, Yang YT, *et al*. Research progress on the mechanism of acupuncture and moxibustion in the treatment of dry eye. *Shanghai J Acu-Mox* 2021;40:219–25.
13 Yang Y, Zhang D, Wu L, *et al*. Electroacupuncture inhibits the corneal ROS/TXNIP/Nlrp3 signaling pathway in a rat model of dry eye syndrome. *Acupunct Med* 2022;40:78–88.
14 Ding N, Wei Q, Deng W, *et al*. Electroacupuncture alleviates inflammation of dry eye diseases by regulating the A7Nachr/NF-KB signaling pathway. *Oxid Med Cell Longev* 2021;2021:6673610.
15 Dhaliwal DK, Zhou S, Samudre SS, *et al*. Acupuncture and dry eye: current perspectives. A double-blinded randomized controlled trial and review of the literature. *Clin Ophthalmol* 2019;13:731–40.
16 Kim T-H, Kang JW, Kim KH, *et al*. Acupuncture for the treatment of dry eye: a multicenter randomised controlled trial with active comparison intervention (artificial teardrops). *PLoS One* 2012;7:e36638.
17 Yang G, Kong X, Guo X, *et al*. Effects of electroacupuncture on dry eye: a pilot randomized controlled trial. *Acta Ophthalmol* 2023;101:e315–26.
18 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
19 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726–32.
20 MacPherson H, Altman DG, Hammerschlag R, *et al*. Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;7:e1000261.
21 Wolffsohn JS, Arita R, Chalmers R, *et al*. TFOS DEWS II diagnostic methodology report. *Ocul Surf* 2017;15:539–74.
22 Borkovec TD, Nau SD. Credibility of analogue therapy rationales. J Behav Ther Exp Psychiatry 1972;3:257–60.
23 Vincent CA. The methodology of controlled trials of acupuncture. *Acupunct Med* 1989;6:9–13.
24 Zhang D, Zhao Y, Yang Y-T, *et al*. A mechanism study of electroacupuncture for dry eye syndrome by targeting conjunctival cytokine expressions. *Curr Eye Res* 2020;45:419–27.
25 WHO Regional Office for the Western Pacific. *WHO Standard Acupuncture Point Locations in the Western Pacific Region*. Manila: World Health Organization, 2008.
26 General Administration of Quality Supervision Inspection and Quarantine of the People's Republic of China, Standardization Administration of the People's Republic of China. *Standardized Manipulations of Acupuncture and Moxibustion—Part 11: Electroacupuncture (GB/T 21709.11-2009)*. China: Standards Press of China, 2009.
27 Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;352:364–5.
28 Zheng B, Liu X-J, Sun Y-QF, *et al*. Development and validation of the Chinese version of dry eye related quality of life scale. *Health Qual Life Outcomes* 2017;15:145.
29 Wang Y, Xu Z, Gong Q, *et al*. The role of different tear volume detection methods in the evaluation and diagnosis of mild dry eye disease. *Transl Vis Sci Technol* 2022;11:15.
30 Jones L, Downie LE, Korb D, *et al*. TFOS DEWS II management and therapy report. *Ocul Surf* 2017;15:575–628.
31 Acet Y, Çil B, Kabak M, *et al*. Instability of tear film after novel coronavirus disease: a noninvasive and no contact method by a Scheimpflug-Placido disc topographer. *Klin Monbl Augenheilkd* 2022;239:338–45.
32 Lum E, Golebiowski B, Swarbrick HA. Reduced corneal sensitivity and sub-basal nerve density in long-term orthokeratology lens wear. *Eye Contact Lens* 2017;43:218–24.
33 Patel S, Mittal R, Sarantopoulos KD, *et al*. Neuropathic ocular surface pain: emerging drug targets and therapeutic implications. *Expert Opin Ther Targets* 2022;26:681–95.
34 Kaštelan S, Bakija I, Bogadi M, *et al*. Psychiatric disorders and dry eye disease - a transdisciplinary approach. *Psychiatr Danub* 2021;33:580–7.
35 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
36 Spitzer RL, Kroenke K, Williams JBW, *et al*. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–7.
37 Basilious A, Xu CY, Malvankar-Mehta MS. Dry eye disease and psychiatric disorders: a systematic review and meta-analysis. *Eur J Ophthalmol* 2022;32:1872–89.
38 Bron AJ, de Paiva CS, Chauhan SK, *et al*. TFOS DEWS II pathophysiology report. *Ocul Surf* 2017;15:438–510.
39 Guerrero-Moreno A, Baudouin C, Melik Parsadaniantz S, *et al*. Morphological and functional changes of corneal nerves and their contribution to peripheral and central sensory abnormalities. *Front Cell Neurosci* 2020;14:610342.
40 Jing D, Liu Y, Chou Y, *et al*. Change patterns in the corneal sub-basal nerve and corneal aberrations in patients with dry eye disease: an artificial intelligence analysis. *Exp Eye Res* 2022;215:108851.
41 Giannaccare G, Pellegrini M, Sebastiani S, *et al*. In vivo confocal microscopy morphometric analysis of corneal subbasal nerve plexus in dry eye disease using newly developed fully automated system. *Graefes Arch Clin Exp Ophthalmol* 2019;257:583–9.
42 Cox SM, Kheirkhah A, Aggarwal S, *et al*. Alterations in corneal nerves in different subtypes of dry eye disease: an in vivo confocal microscopy study. *Ocul Surf* 2021;22:135–42.
43 Liu Y, Chou Y, Dong X, *et al*. Corneal subbasal nerve analysis using in vivo confocal microscopy in patients with dry eye: analysis and clinical correlations. *Cornea* 2019;38:1253–8.
44 Ma J, Wei S, Jiang X, *et al*. Evaluation of objective visual quality in dry eye disease and corneal nerve changes. *Int Ophthalmol* 2020;40:2995–3004.
45 Kheirkhah A, Rahimi Darabad R, Cruzat A, *et al*. Corneal epithelial immune dendritic cell alterations in subtypes of dry eye disease: a pilot in vivo confocal microscopic study. *Invest Ophthalmol Vis Sci* 2015;56:7179–85.
46 Lan W, Tong L. Acupuncture has effect on increasing tear break-up time: acupuncture for treating dry eye, a randomized placebo-controlled trial. *Acta Ophthalmol* 2012;90:e73.
47 Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 2019.
48 Ying G-S, Maguire MG, Glynn RJ, *et al*. Tutorial on biostatistics: longitudinal analysis of correlated continuous eye data. *Ophthalmic Epidemiol* 2021;28:3–20.
49 Ying G-S, Maguire MG, Glynn R, *et al*. Tutorial on biostatistics: statistical analysis for correlated binary eye dat. *Ophthalmic Epidemiol* 2018;25:1–12.
50 Ying G-S, Maguire MG, Glynn R, *et al*. Tutorial on biostatistics: linear regression analysis of continuous correlated eye data. *Ophthalmic Epidemiol* 2017;24:130–40.
51 Wei Q-B, Ding N, Wang J-J, *et al*. Acupoint selection for the treatment of dry eye: a systematic review and meta-analysis of randomized controlled trials. *Exp Ther Med* 2020;19:2851–60.
52 Lin Y-H, Wu H-C, Hsieh P-C, *et al*. An association rule analysis of combined acupoints for the treatment of patients with dry eye disease. *Complement Med Res* 2021;28:317–24.
53 Intriago V, Reina MA, Boezaart AP, *et al*. Microscopy of structures surrounding typical acupoints used in clinical practice and electron microscopic evaluation of acupuncture needles. *Clin Anat* 2022;35:392–403.
54 Chen Z-X, Li Y, Zhang X-G, *et al*. Sham electroacupuncture methods in randomized controlled trials. *Sci Rep* 2017;7:40837.
55 Lund I, Näslund J, Lundeberg T. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: a physiologist's perspective. *Chin Med* 2009;4:1.
56 Moffet HH. Sham acupuncture may be as efficacious as true acupuncture: a systematic review of clinical trials. *J Altern Complement Med* 2009;15:213–6.
57 Vickers AJ, Vertosick EA, Lewith G, *et al*. Acupuncture for chronic pain: update of an individual patient data meta-analysis. *J Pain* 2018;19:455–74.
58 Birch S, Lee MS, Kim T-H, *et al*. Historical perspectives on using sham acupuncture in acupuncture clinical trials. *Integr Med Res* 2022;11:100725.
59 Zucker NA, Tsodikov A, Mist SD, *et al*. Evoked pressure pain sensitivity is associated with differential analgesic response to verum and sham acupuncture in fibromyalgia. *Pain Med* 2017;18:1582–92.
60 Harris RE, Zubieta J-K, Scott DJ, *et al*. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). *Neuroimage* 2009;47:1077–85.