The efficacy and safety of acupuncture or combined with western medicine for dry eye
A protocol for systematic review and meta-analysis

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Abstract

Background: As a traditional Chinese medicine external treatment method, acupuncture is characterized by simple operation, significant treatment effect and few side effects. Dry eye, also known as conjunctival xerosis, refers to pathological changes in tissues of ocular surface caused by abnormal tear quality and quantity or dynamics due to various reasons, which can cause red and swollen eyes, congestion, and severe cases may result in lesions of the conjunctiva. Clinical practice shows that acupuncture has a certain therapeutic effect on dry eye, but there is a lack of medical evidence. The objective of the research carried out in this program is to evaluate the effectiveness and safety of acupuncture combined with western medicine in the treatment of dry eye.

Methods: Computer retrieval English database (PubMed, Embase, Web of Science, the Cochrane Library) and Chinese database (CNKI, WF, VIP, CBMDISC), moreover manual retrieval of clinical research on the treatment of dry eyes by acupuncture in combination with western medicine from Baidu academic and Google Academic from database building to May 2020, the quality included in the study was evaluated and data extraction was completed by 2 independent researchers. RevMan5.3 software was utilized for meta-analysis to the included literature.

Results: In this study, the effectiveness and safety of acupuncture combined with western medicine in the treatment of dry eye were evaluated by several indicators, such as the score of the ocular surface disease index, the amount of tear secretion and the tear film rupture time.

Conclusions: This study will provide reliable evidence for the clinical application of acupuncture combined with western medicine in the treatment of dry eyes.

OSF Registration number: DOI 10.17605/OSF.IO/5DJ9W.

Abbreviations: BUT = Tear break-up time, CI = confidence interval.

Keywords: acupuncture, dry eye, meta-analysis, protocol, systematic review
without any toxic effects. Therefore, it has certain advantages in clinical practice.[6]

At present there are multiple randomized controlled study results show that, acupuncture has a significant effect on dry eye with high cure rate, low recurrence rate and less adverse reaction, but there exist great differences in the design and efficacy of clinical study, leading to the uneven results. To a certain extent, that affects the reliability of the study results and the promotion of the therapy. Therefore, the objective of the study is to evaluate the efficacy and safety of acupuncture alone or combined with western medicine in the treatment of dry eye, so as to provide a reliable basis for the clinical treatment of dry eye with acupuncture.

2. Methods

2.1. Protocol register

This protocol of systematic review and meta-analysis has been drafted under the guidance of the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P). Moreover, it has been registered on open science framework (OSF) on July 21, 2020 (Registration number: DOI 10.17605/OSF.IO/5DJ9W).

2.2. Ethics

Since this is a protocol with no patient recruitment and personal information collection, the approval of the ethics committee is not required.

2.3. Eligibility criteria

2.3.1. Types of studies. We will collect all available randomized controlled trails on acupuncture treatment for dry eye, regardless of blinding, publication status, region, but Language will be restricted to Chinese and English.

2.3.2. Objects of the study. Patients definitely diagnosed with dry eye but without other complications, including their nationality, race, age, sex, course of disease and pathogenic site

2.3.3. Intervention. The treatment group was treated by filiform needle acupuncture combined with western medicine, including acupuncture and acupuncture combined with western medicine. There were no restrictions on filiform needle acupuncture techniques and acupoints; the control group was treated by western medicine alone where type, dose and course of treatment were not defined.

2.3.4. Outcome indicator.

(1) Primary outcome: Ocular surface disease index;
(2) Secondary outcomes: Schirmer test, Tear break-up time, lactoferrin in tears, Visual analogue scale, Incidence of adverse reactions.

2.4. Exclusion criteria

(1) Study published repeatedly;
(2) Study whose literature is abstract and conference papers, in which the original data cannot be obtained;
(3) Study whose data is incomplete or where there are obvious errors that cannot be handled after contacting the author;
(4) Study with wrong random method;
(5) Study where the filiform acupuncture therapies are not used in the treatment group, such as ear acupuncture, moxibustion and acupoint application;
(6) The control group in which the treatment is done by traditional Chinese and western medicine.

2.5. Search strategy

The “acupuncture,” “needling,” and “dry eye” were used as Chinese terms to search in Chinese databases, including China Knowledge Network (CNKI), Wanfang Data Knowledge Service Platform, VIP Information Chinese Journal Service Platform (VIP), China Biomedical Database; “acupuncture,” “needling,” “dry eye,” used as English terms to search in English databases, including PubMed, EMBASE, Web of Science, the Cochrane Library, and manually search in Baidu academics and Google academics. The retrieval time was from the establishment of the database to July 2020, before all domestic and foreign literatures on the treatment of dry eye with filiform needle acupuncture were collected. Taking PubMed as an example, the search strategy is shown in Table 1.

2.6. Data screening and extraction

Cochrane Collaboration System Reviewer Manual Version 5.0 was used as a reference for the method of selection in the study. According to the PRISMA flow chart, EndNote X7 document management software was utilized by 2 researchers to independently screen the documents based on the above inclusion and exclusion criteria before mutual check. Those difficult to determine whether included in the study, would be discussed and judged with a third researcher. At the same time, Excel 2013 was used to extract relevant information, including:

1. Clinical research (title, first author, publication year and month, sample size, sex ratio, average age, average course of disease);
2. Intervention measures (name of western medicine used in the control group, dosage, course of treatment; acupuncture points, frequency of acupuncture and course of treatment used in the treatment group);
3. Evaluation factors of risk bias in randomized controlled studies;
4. Observation indicators. The literature screening process is shown in Figure 1.

2.7. Literature quality evaluation

Built-in Risk bias evaluation tool of Review Manager 5.3 Software (the Cochrane collaboration’s tool for assessing risk of

| Table 1 |
| Search strategy in PubMed database. |
| Number | Search terms |
|---|---|
| #1 | Acupuncture[MeSH] |
| #2 | Acupuncture[Title/Abstract] |
| #3 | Pharmacopuncture[Title/Abstract] |
| #4 | Needling[Title/Abstract] |
| #5 | pinprick[Title/Abstract] |
| #6 | #1 OR #2 OR #3 OR #4 OR #5 |
| #7 | Dry eye syndrome[Mesh] |
| #8 | Dry eye syndrome[Title/Abstract] |
| #9 | Dry eye [Title/Abstract] |
| #10 | #7 OR #8 OR #9 |
| #11 | #6 AND #10 |
bias) was used to assess the risk bias in the included studies. Two researchers determined the literatures from 3 levels, including low-risk, unclear, and high-risk based on the performance of the included literature in the above evaluation items. After completion, they would recheck. In case of a disagreement, they would discuss. If no agreement could be reached, a decision would be made in consultation with researchers from the third party.

2.8. Statistical analysis

2.8.1. Data analysis and processing. The RevMan 5.3 software provided by the Cochrane Collaboration was used for statistical analysis.

1. For dichotomous variables, relative risk was used for statistics. For continuous variables, Weighted Mean Difference was selected when the tools and units of measurement indicators are the same, Standardized Mean Difference was selected with different tools or units of measurement, and all the above were represented by effect value and 95% confidence interval (CI).

2. Heterogeneity test: Q test was used to qualitatively determine inter-study heterogeneity. If $P \geq .1$, there was no inter-study heterogeneity, If $P < .1$, it indicated inter-study heterogeneity.

At the same time, $I^2$ value was used to quantitatively evaluate the inter-study heterogeneity. If $I^2 \leq 50\%$, the heterogeneity was considered to be good, and the fixed-effect model was adopted. If
The commonly used acupoints are DU20 (Baihui), EX-HN5 (Taiyang), BL2 (Cuanzhui), BL1 (Jingming), GB1 (Tongzhi Liao), ST1 (Chengqi), ST2 (Sibai), LI20 (Yingxiang), LT4 (Hegu), SP6 (Sanyinjiao), ST36 (Zusanli) and so on. The DU20 (Baihui) will be through the governor and conception vessels, smoothing vital essence. The EX-HN5 (Taiyang), BL2 (Cuanzhui), BL1 (Jingming), GB1 (Tongzhi Liao) are local acupoints, which can improve ocular symptoms. ST1 (Chengqi), ST2 (Sibai) can regulate the Qi and blood around the eyes; LI20 (Yingxiang) is the intersection point of the hand and foot Yangming meridian, which can adjust the 2 meridians and dredge wind and heat. LT4 (Hegu) is the original point of large intestine meridian of Hand Yangming, which can regulate qi and activate blood circulation. Distal acupoint selection: SP6 (Sanyinjiao), GB37 (Guangming), ST36 (Zusanli), etc. SP6 (Sanyinjiao) can nourish liver and kidney, harmonize Qi and blood. GB37 (Guangming) can smooth obstructions in liver and gallbladder meridians, harmonize Qi and blood, control the good treatment of various eye diseases. ST36 (Zusanli) is a stomach cooperation point, which plays a role in strengthening the body.12,13

Clinical studies have shown that acupuncture can affect the expression of lactoferrin in tears and mucoprotein, induce the quantitative changes in some proteins of tears,14 effectively inhibit the inflammatory response of dry eyes, prolong rupture time of tear film, and enhance the stability of tear film.15,16 Acupuncture can affect the tissue morphology of functional units, restore damaged corneal tissue, improve dry corneal morphology, and promote the rehabilitation of ocular surface structures.17 Acupuncture can adjust the level of hormones and regulate the related functions of ocular surface hormone receptors.24 Acupuncture can regulate the blood circulation around the eyes, promote self-repair of eye tissues, improve ocular symptoms,25 adjust the quality and quantity of tears, and improve the ocular microenvironment.24 It is worth noting that during the treatment of Dry Eye by acupuncture, operators shall pay attention to the depth and technique of acupuncture when needling on the points, such as Jingming and Chengqi. Acupuncture should not be too deep or violent to avoid puncturing blood vessels and causing hematoma.

At present, acupuncture therapy alone or combined western medicine for the treatment of dry eye in randomized controlled study was widely reported, but lacking in systematic and correct evaluation. Therefore, it is necessary to objectively evaluate the clinical effectiveness and safety of acupuncture in the treatment of Dry Eye through evidence-based medicine, so as to provide a reliable basis for clinical doctors to take acupuncture in the treatment of Dry Eye and to reduce the adverse reactions of western medicine treatment. However, this study also has some limitations, since the simulate operation is difficult to achieve, it is difficult to implement the blind method. The different acupoints...
of acupuncture have certain influence on the study results. At the same time, only English and Chinese literature were searched due to the limitation on languages. Studies in other languages were ignored, which might lead to certain publication bias.

**Author contributions**

Data collection: Hongyi Lan and Yanjin Song.
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Writing – original draft: Xu Wang and Yihua Fan.
Writing – review & editing: Xu Wang and Zhillong Zhang.

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