The efficacy of traditional Chinese medicine for treatment of dry eye symptom: a meta-analysis

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Abstract: Objective: This study aims to systematically review the efficacy of Traditional Chinese Medicine (TCM) for treatment of dry eye symptom (DES). Methods: PubMed, EMBase, MEDLINE, The Cochrane Library, VIP, CNKI, CBM and Wanfang databases were searched manually and automatically by computer. The published literatures about DES treated by TCM were collected. After selection, quality evaluation and data extraction by two researchers, RevMan 5.2 was applied for Meta-analysis. Results: Totally 18 randomized controlled trials were included in this study based on our screening criteria. The meta-analysis results showed that TCM was better in improving ocular symptoms than control drugs, and the difference of total efficacy rate between TCM group and control group was statistically significant (OR = 3.66, 95% CI [2.80, 4.78], P<0.00001). For increasing the amount of tear secretion, TCM was significantly superior to control (WMD = 1.58, 95% CI [1.01, 2.16], P<0.00001). The break-up time of tear film was extended in TCM group than in control group (WMD = 1.32, 95% CI [0.93, 1.71], P<0.00001). Conclusion: TCM treatment for DES can significantly improve ocular symptoms, increase the amount of tear secretion, and extend the break-up time of tear film, which indicates that the efficacy in TCM group is better than in control group. As the good quality of associated studies is lacking and the publication bias is existed, the conclusion in this study needs further validation by better designed clinical randomized controlled trails.

Keywords: Traditional Chinese medicine, randomized controlled trial, ZEB2, meta-analysis

Introduction

Dry eye symptom (DES) is a general term of a group of diseases in eyes characterized with discomfort and/or ocular tissue lesions, which had abnormal quality or quantity of tear and decreased stability of tear film [1]. The clinical manifestations include dryness, visual fatigue, foreign body sensation, burning sensation, red eye, photophobia, and soreness [2]. The morbidity of DES is increased gradually and demonstrates younger trend. Among the reported epidemiological survey, the prevalence of DES is different as the different population, diagnosis criteria, and clinical environment. Sehaumberg et al. reported that the prevalence rate of DES was about 7.8% among 40,000 American women [3]. Lee et al. showed that the morbidity was about 27.5% for Indonesia residents [4]. Currently, the main treatment for DES is using artificial tears to relieve the symptoms, which can’t resolve problems in etiology.

DES is regarded as “white astringent”, “Shen Shui will dry”, “Shen Shui weary dry”, and “dryness syndrome” by TCM. The treatment for DES by TCM mainly includes internal medicine, acupuncture, fumigation, and eye drops. Many clinical reports showed that it was effective about TCM for treatment of DES, and TCM was better than Western medicine [5]. However, strong supportive evidences are lack, especially for the systematic evaluation of TCM (non-proprietary). In this study, we applied Cochrane method to collect and systematically evaluate the clinical randomized controlled trails about TCM and Western medicine for treatment of DES. Based on objectively evaluating the clinical effect of DES, the meta-analysis results can provide reliable evidence for clinical application.

Methods

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Article type: randomized controlled trials were included. (2) Subjects: patients who were diagnosed with DES were included and there was no limi-
Traditional Chinese medicine for dry eye symptom

Articles identified through database searching
(n = 103)

Articles excluded through titles and abstracts
(n = 72)

Initially identified articles
(n = 31)

--- non-randomized controlled trials (n=8)
--- articles failed to meet the inclusion criteria (n=3)
--- articles with incomplete data (n=2)

Articles included in meta-analysis
(n = 18)

Figure 1. Flowchart of study selection.

Inclusion criteria were as follows: (1) Review articles were excluded. (2) Articles about animal experiments were excluded. (3) Articles with incomplete original data were excluded.

Search strategy

Computer-based retrieval method was applied to search PubMed (1966-Oct. 2015), EMBase (1974-Oct. 2015), Cochrane (1974-Oct. 2015), VIP (1989-Oct. 2015), CNKI (1994-Oct. 2015), CBM (1978-Oct. 2015) and Wanfang database. Relevant studies were identified using the following key words and subject terms: “Dry eye” or “Dry eye symptom” or “Xerophthalmia” or “kerato-conjunctivitis sicca”. At the same time, “Traditional Chinese Medicine” or “Integrative Medicine” was used as uncontrolled terms to do literature search. All the searching strategies were finalized after several pre-searching. In addition, relevant literatures and cited references were found from Internet by Google Scholar, Medical matrix and other searching engine. The relevant information that we can’t get by above searching strategy was obtained by contacting with experts and correspondence authors in this field.

Literature screening

Two researchers cross-checked the results of included studies according to the inclusion and exclusion criteria. Any encountered discrepancies were resolved by discussion with a third party. The absent information was supplemented through contact with authors with call or Email.

Data extraction and quality evaluation

Two researchers independently extracted trial associated data and cross-checked each other. The main content includes: (1) Basic materials: title, author name, publication date, and literature source; (2) Research characteristic: general condition of objects in studies, baseline of patients in different groups, and intervention measures; (3) Endpoints. Any encountered discrepancies were resolved by discussion with a third researcher. The methodology in each RCT was evaluated based on the evaluation criteria in Cochrane handbook 5.2 (Random allocation method, allocation concealment, blind implementation, data integrity of results, losing follow-up, and quit). If the cases of lost follow-up are more than 20% of total cases, the possible causes for losing should be further analyze, and intention to treat (ITT) was applied to analyze. The Jadad rating scale [7] was used to score the quality of inclusion studies, score 0-2 is for low-quality research, score 3-5 is for high quality. If literature number for combined analysis is more than 10, the funnel plot by RevMan 5.2 software is used to estimate the publication bias.
## Table 1. Evaluation of included literature

<table>
<thead>
<tr>
<th>Included literature</th>
<th>Publication year</th>
<th>Grouping</th>
<th>Case Number</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Treatment course</th>
<th>Jadad scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guixia Zhao [9]</td>
<td>1999</td>
<td>Random words</td>
<td>60/60</td>
<td>Yi Shen Yang Mu Tang</td>
<td>brombexine hydrochloride</td>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td>Jianfeng Chen [10]</td>
<td>2007</td>
<td>Registration order</td>
<td>40/40</td>
<td>Ba Wu Tang</td>
<td>Tear Naturals II (TN-II)</td>
<td>2 months</td>
<td>1</td>
</tr>
<tr>
<td>Xiaojuan Lai [12]</td>
<td>2008</td>
<td>Stratified block randomization</td>
<td>30/30</td>
<td>Run Zao Ming Mu Tang</td>
<td>Tear Naturals II (TN-II)</td>
<td>1 month</td>
<td>2</td>
</tr>
<tr>
<td>Jinglan Lin [13]</td>
<td>2008</td>
<td>Registration order</td>
<td>28/28</td>
<td>Qi Ju Di Huang Tang</td>
<td>0.1% Sodium Hyaluronate Eye Drops</td>
<td>2 months</td>
<td>1</td>
</tr>
<tr>
<td>Xiaoqun Ye [14]</td>
<td>2008</td>
<td>Random words</td>
<td>30/30</td>
<td>Yi Qi Zi Yin Run Mu Tang</td>
<td>0.1% sodium hyaluronate eye drops</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Xiuhua Xu [11]</td>
<td>2007</td>
<td>Random words</td>
<td>40/40</td>
<td>Run Zao Ming Mu Tang</td>
<td>Tear Naturals II (TN-II)</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Li Song [15]</td>
<td>2008</td>
<td>Random grouping</td>
<td>24/20</td>
<td>Ming Mu Di Huang Wan</td>
<td>Sodium Hyaluronate Eye Drops</td>
<td>1 month</td>
<td>2</td>
</tr>
<tr>
<td>Hongxia Zhao [16]</td>
<td>2008</td>
<td>Random words</td>
<td>30/30</td>
<td>Yang Yin Qing Fei Tang</td>
<td>Routine artificial tears + VitA</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Yan Chen [17]</td>
<td>2008</td>
<td>Registration order</td>
<td>62/67</td>
<td>ZiShui Ming Mu Tang</td>
<td>VitAD + VitB2 + Fibroblast Growth Factor in Eye Drop</td>
<td>2 months</td>
<td>1</td>
</tr>
<tr>
<td>Xiaoli Ma [18]</td>
<td>2009</td>
<td>Random number table</td>
<td>30/30</td>
<td>Ping Gan Yi Jing Fang</td>
<td>Routine artificial tears</td>
<td>1 month</td>
<td>3</td>
</tr>
<tr>
<td>Lishun Zhou [19]</td>
<td>2008</td>
<td>Random words</td>
<td>40/30</td>
<td>Yang Yin Run Mu Tang</td>
<td>ZhenzhuMingmu eye drops</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Yanhong Xu [20]</td>
<td>2009</td>
<td>Random words</td>
<td>25/25</td>
<td>Run Mu Ling aerosol inhalation</td>
<td>Injection Water</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Xuezhang Zhao [21]</td>
<td>2009</td>
<td>Random words</td>
<td>30/30</td>
<td>TCM</td>
<td>Tear Naturals II (TN-II)</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Feng Xu [22]</td>
<td>2009</td>
<td>Random number table</td>
<td>100/100</td>
<td>Long Dan Ming Mu Pian</td>
<td>0.1% sodium hyaluronate eye drops</td>
<td>1 month</td>
<td>3</td>
</tr>
<tr>
<td>Kai Li [23]</td>
<td>2009</td>
<td>Random words</td>
<td>37/38</td>
<td>Run Mu Ling</td>
<td>Placebo</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>FajieKe [24]</td>
<td>2010</td>
<td>Random words</td>
<td>50/48</td>
<td>Qi Ju Di Huang Wan</td>
<td>Tear Naturals II (TN-II)</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Chaoying Wang [25]</td>
<td>2010</td>
<td>Random words</td>
<td>78/70</td>
<td>Bu Gan Yang Yin Tang + 0.1% sodium hyaluronate eye drops + Antibiotic</td>
<td>0.1% sodium hyaluronate eye drops + Antibiotic</td>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td>Yulan Li [26]</td>
<td>2014</td>
<td>Random words</td>
<td>40/40</td>
<td>TCM ultrasonic spray</td>
<td>0.1% Sodium Hyaluronate Eye Drops</td>
<td>0.5 months</td>
<td>1</td>
</tr>
</tbody>
</table>
Traditional Chinese medicine for dry eye symptom

Statistical analysis

Meta-analysis was performed using the Cochrane Collaboration RevMan 5.2 software [8]. For enumeration data, the Odds Ratio (OR) was used, while the weighted mean difference (WMD) was applied for measurement data, and each effect variable was expressed in 95% CI. A \( \chi^2 \)-test statistic was performed to assess the heterogeneity among studies. When \( I^2 < 50\% \) and \( P > 0.1 \), a fixed effects model was used to do combined analysis. If heterogeneity was significant (\( I^2 > 50\% \) and \( P < 0.1 \)), causes of heterogeneity should be analyzed to determine whether random effect model can be used. If clinical heterogeneity is obvious among studies, only descriptive analysis is considered. When necessary, sensitivity analysis will be used to analyze the stability of results.

Results

Quality evaluation of included studies

According to the searching strategy, 103 relevant literatures were selected (Figure 1). After reading titles and abstracts, 72 papers were excluded and 31 papers were included. After exclusion of 8 non-randomized controlled trials, 3 papers that failed to meet the inclusion criteria, and 2 literatures with data incompleteness, 18 RCTs were included in this meta-analysis [9-26]. All the included literatures showed that baseline data between two groups were comparable through statistical analysis. All 18 studies applied randomization designating, among which 2 studies [13, 17] used random number table, 2 studies [20, 23] used stratified random grouping method, 3 studies [18, 22, 25] used semi-random method depending on treatment order, and the remaining 11 studies just mentioned “randomly divided into two groups”.

About intervention in control group, artificial tears were used for routine treatment in 15 studies except for 3 literatures [15, 22, 26]. During treatment, majorities of studies were within 1 month. Through Jadad scale analysis, only 2 studies [13, 17] among 18 studies belonged to high-quality research, the details were shown in Table 1.

Difference analysis of BUT before and after treatment

There were 7 studies that compared the break-up time of tear film in TCM treatment group and control group, and total 609 eyes were included. It was shown that heterogeneity test was not statistical significance. The fixed effect model was used to do meta-analysis. The results showed that there was significant difference (WMD = 1.32, 95% CI [0.93, 1.71], \( P < 0.00001 \)) between TCM group and control group. This indicated that the extension of BUT was longer in patients treated with TCM than control artificial tears, as shown in Figure 2.

Schirmer test before and after treatment

There were 6 studies that compared the quantity of tear fluid in TCM treatment group and control group before and after treatment, and total 549 eyes were included. Heterogeneity test showed no statistical significance, so the fixed effect model was used to do meta-analysis. The results showed that there was significant difference (WMD = 1.58, 95% CI [1.01, 2.16], \( P < 0.00001 \)) between TCM group and control group. This indicated that the increasing amount of tear fluid was longer in TCM group than in control group. The details were shown in Figure 3.
Comparison of overall response rate

There were 17 studies that compared the total effective rate in TCM treatment group and control group. Heterogeneity test showed no statistical significance, so the fixed effect model was used to do meta-analysis. The results showed that there was significant difference (WMD = 1.58, 95% CI [1.01, 2.16], P<0.00001) between TCM group and control group for the overall response rate, which indicated that the effect was better for patients treated with TCM group. The Meta-analysis results were shown in Figure 4.

Evaluation of publication bias

To assess the risk of publication bias, the funnel plot about overall response rate was generated. As shown in Figure 5, the funnel plot demonstrated a skewed distribution and concentrated in the top region, which indicated some possibilities of publication bias for the Meta-analyses.

Discussion

DES is a general term for different kinds of diseases in eyes caused by different factors, which is characterized with discomfort and ocular tissue lesions when the tear film is un-stability and kinetics is abnormal. DES can induce dryness, foreign body sensation, burning sensation, photophobia, blurred vision, vision loss even blindness [1, 2]. In TCM, it is believed that deficiency of liver-yin and kidney-yin, endogenous hot, and the theory of body fluid and blood being derived from the same source are the
Traditional Chinese medicine for dry eye symptom

Figure 5. The funnel plot about the total efficiency of TCM to treat dry eye symptom.

cause of DES. The characteristic of DES is deficient root and excessive superficial, deficient root determines deficiency of liver-yin and kidney-yin, and excessive superficial determines disorder of hot blood [5]. In this paper, we applied Meta-analysis method to evaluate the total efficacy of TCM to treat DES. The results indicated that TCM significantly improved eye symptoms, increased quantity of secreted tear, extended BUT when compared with control group.

Although several literatures and clinical studies about TCM were recognized by modern medicine, the efficacy of TCM can’t be easily evaluated as independent study, small size of cases, different criteria in treatment methods and estimation. Summarizing the most confident evidences from large amount of literatures is the most important issue to be resolved for physicians. Evaluation of clinical studies about TCM to treat DES can not only comprehensively understand the problems about designing, implementation, and efficacy, but also recognize the clinical application value of TCM in treatment of DES. Though discussing the advantage and disadvantage of TCM, this study provides reference and theoretical basis for guiding clinical medicine and improving the quality of literature.

However, the result objectivity of systematic review should be based on high quality RCTs. Based on the evaluation of Meta-analysis on TCM to treat DES, we can see that many included studies are low quality, and multi-center clinical studies are lack. As to random, blindness, and follow-up, the key designing is not strictly followed the medicine criteria. The selection, estimation, and balance of patients are not in attention, and the description of statistical details is lack. In this study, the funnel plot was used to reflect the distribution of clinical research data. It was shown that Meta-analysis of included studies demonstrated inverted funnel and skewed distribution and enriched in top funnel, which indicated that publication bias may exist. Secondly, the conclusion from the 26 included studies emphasized more on positive, which may be another reason for publication bias. The difference of treatment course and follow-up may also induce a certain extent of bias. All these reasons may lead to the relative low quality of Meta-analysis and low confidence of evidence.

In summary, based on current research, TCM can significantly improve eye symptoms, increase quantity of secreted tear, extend BUT for treatment DES. As the insufficient high quality RCTs and publication bias, more well-designed randomized controlled trials are needed to further confirm the efficacy of TCM for DES.

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Disclosure of conflict of interest

None.

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Traditional Chinese medicine for dry eye symptom

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