Original Article
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. Sehaum-berg et al. reported that the prevalence rate of DES was about 7.8% among 40000 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 "dry-ness 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-
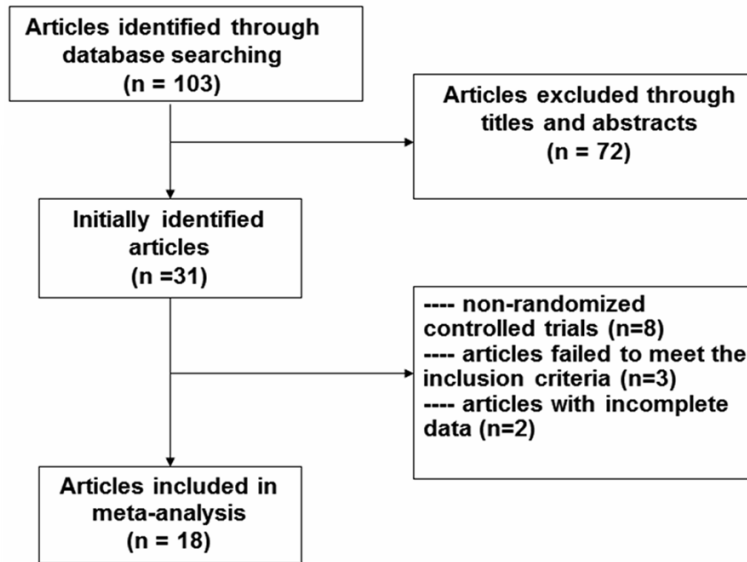
Figure 1. Flowchart of study selection.

tation in gender organ. The applied diagnosis criteria were mainly referenced to the "TCM Syndrome Diagnostic efficacy standards" promulgated by the State Administration of Traditional Chinese Medicine [6]. (3) Intervention measures: artificial tears in combination with TCM or TCM alone were used in treatment group, while artificial tears alone were used in control group. (4) Main endpoints include breakup time for tear film (BUT), the quantity of tear fluid (Schirmer I test), and total efficacy rate for improving eye symptoms (Clinical symptoms, tear secretion, BUT, and corneal fluorescein staining, overall response rate = number of effective/total cases).

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 trail 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

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

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Lai 2008	6.37	1.92	30	5.23	2.22	30	13.3%	1.14 [0.09, 2.19]	
Li 2009	3.61	1.93	37	2.89	1.49	38	24.0%	0.72 [-0.06, 1.50]	
Song 2008	5.23	2.76	48	4.83	3.08	40	9.6%	0.40 [-0.83, 1.63]	
Xu 2007	6.82	4.84	80	5.31	3.42	80	8.7%	1.51 [0.21, 2.81]	
Xuyan2009	4.63	2.21	50	2.89	1.77	46	23.0%	1.74 [0.94, 2.54]	
Zhao 1999	9.18	1.46	30	7.72	3.54	30	7.8%	1.46 [0.09, 2.83]	
Zhou 2008	7.46	2.67	40	5.12	1.76	30	13.6%	2.34 [1.30, 3.38]	
Total (95% CI)			315			294	100.0%	1.33 [0.94, 1.71]	

Heterogeneity: Chi² = 9.40, df = 6 (P = 0.15); I² = 36%
Test for overall effect: Z = 6.79 (P < 0.00001)

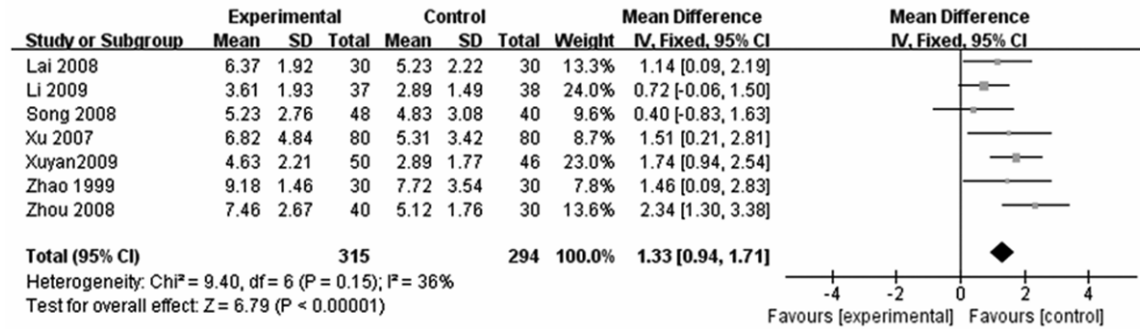Favours [experimental]   Favours [control]

Figure 2. Meta-analysis for break-up time of tear film (BUT) of TCM to treat 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 χ^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 designing, 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 men-

tioned "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, which indicated that the increasing amount of tear fluid was longer in TCM group than in control group. The details were shown in **Figure 3**.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Lai 2008	4.53	1.94	30	3.7	2.1	30	31.2%	0.83 [-0.19, 1.85]	
Li 2009	6.97	6.41	37	5.26	4.42	38	5.2%	1.71 [-0.79, 4.21]	
Song 2008	7.85	6.04	48	6.15	4.14	40	7.2%	1.70 [-0.44, 3.84]	
Xu 2007	8.39	4.27	80	6.83	4.59	80	17.3%	1.56 [0.19, 2.93]	
Xuyan2009	6.44	5.69	50	4.89	3.82	46	8.8%	1.55 [-0.38, 3.48]	
Zhou 2008	7.46	2.67	40	5.12	1.76	30	30.2%	2.34 [1.30, 3.38]	
Total (95% CI)			**285**			**264**	**100.0%**	**1.58 [1.01, 2.16]**	

Heterogeneity: Chi² = 4.14, df = 5 (P = 0.53); I² = 0%
Test for overall effect: Z = 5.43 (P < 0.00001)

Favours [experimental] Favours [control]

Figure 3. Meta-analysis for quantity of tear fluid of TCM to treat dry eye symptom.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Chen 2007	38	40	31	40	2.6%	5.52 [1.11, 27.43]	
Chen 2008	56	62	48	67	7.4%	3.69 [1.37, 10.00]	
Ke 2010	43	50	34	48	8.0%	2.53 [0.92, 6.96]	
Lai 2008	28	30	22	30	2.4%	5.09 [0.98, 26.43]	
Li 2009	32	37	30	39	6.5%	1.92 [0.58, 6.38]	
Li 2014	38	40	26	40	2.1%	10.23 [2.14, 48.85]	
Lin 2008	26	28	21	28	2.5%	4.33 [0.81, 23.10]	
Ma 2009	20	30	17	30	9.3%	1.53 [0.54, 4.36]	
Wang 2010	68	78	47	70	10.5%	3.33 [1.45, 7.63]	
Xu 2007	62	80	50	80	18.6%	2.07 [1.03, 4.13]	
Xu 2009	97	100	69	100	3.4%	14.53 [4.27, 49.43]	
Xuyan2009	18	25	9	25	4.2%	4.57 [1.38, 15.11]	
Ye 2008	27	30	20	30	3.3%	4.50 [1.09, 18.50]	
Zhao 1999	50	60	32	60	8.8%	4.38 [1.87, 10.21]	
Zhao 2008	65	68	60	68	4.4%	2.89 [0.73, 11.40]	
Zhao 2009	29	30	25	30	1.4%	5.80 [0.63, 53.01]	
Zhou 2008	35	40	20	30	4.7%	3.50 [1.05, 11.69]	
Total (95% CI)		**828**		**815**	**100.0%**	**3.66 [2.80, 4.78]**	
Total events	732		561				

Heterogeneity: Chi² = 14.59, df = 16 (P = 0.56); I² = 0%
Test for overall effect: Z = 9.51 (P < 0.00001)

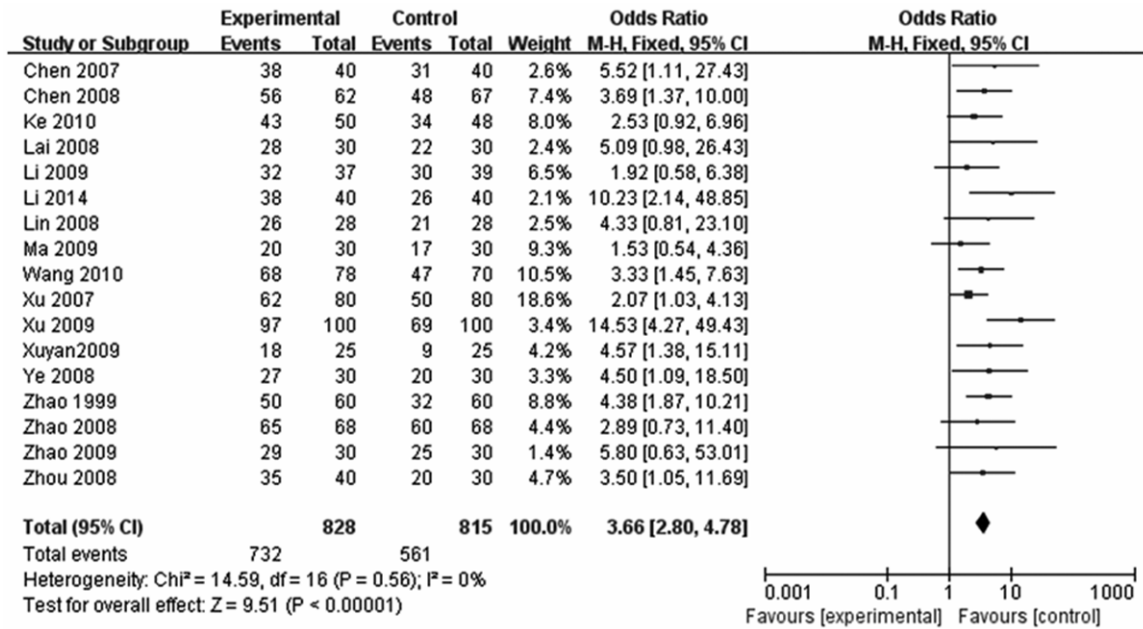Favours [experimental] Favours [control]

Figure 4. Meta-analysis for overall response rate of TCM to treat dry eye symptom.

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 gener-

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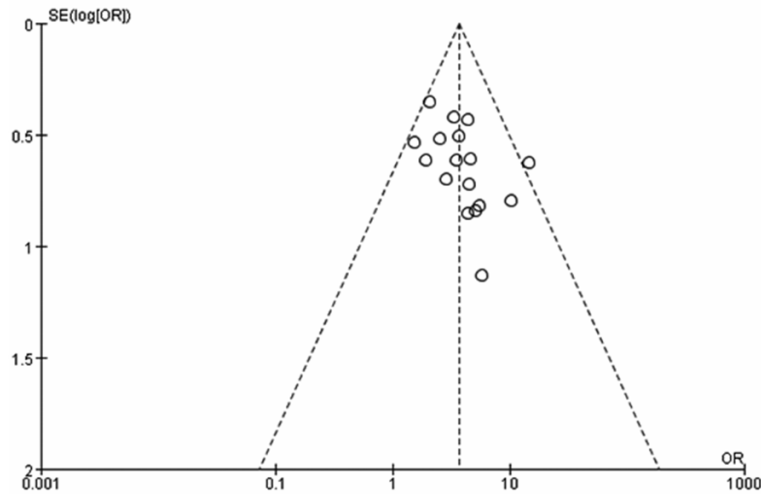
Figure 5. The funnel plot about the total efficiency of TCM to treat dry eye symptom.

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.

Disclosure of conflict of interest

None.

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