Systematic Review and Meta-Analysis

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The clinical efficiency of lycium-rehmannia pills in treating dry eye symptom

A meta-analysis

Lili Lou, MM[a,b,c], Hongling Fu, MM[a,b,c], Hanmin Liu, MD[a,b,c,*]

Abstract

Background: Dry eye symptom threatens human health and causes a larger burden of disease, the study aims to systematically compare the therapeutic effect of Lycium-rehmannia pills combined with topical eye drops and pure western medicine (western medicine eye drops) on dry eye symptom, to provide a reflection and enlightenment for clinical treatment.

Method: PubMed, The Cochrane Library, EMbase, MEDLINE, CBM, WanFang, VIP, and CNKI databases were searched manually and automatically by the computer until March 2019 and relevant randomized controlled trials (RCTs) were selected. Article selection and data extraction were conducted by 2 researchers independently, then RevMan 5.3 was applied for meta-analysis.

Result: Fifteen randomized controlled trials were included, including 1222 patients (eyes = 2382). The meta-analysis results showed that Lycium-rehmannia pills combined with western medicine were superior to the control group in terms of therapeutic efficiency [OR = 4.38, 95% confidence interval (CI) (3.26, 5.89), $P < .00001$]. There were controversial results that the study group was better than the control group in Basic Schirmer test [MD, 2.46, 95% CI (1.49, 3.44), $P < .00001$], tear break up time [MD, 3.79, 95% CI (3.57, 4.01), $P < .00001$], and Fluorescein test [MD, −1.29, 95% CI (−1.42, −1.15), $P < .00001$], but Lycium-rehmannia pills combined with western medicine could not reduce the incidence of adverse reactions, including eyelid inflammation [OR = 1.00, 95% CI (0.37, 2.72), $P = 1.00$] and congestion symptom [OR = 0.55, 95% CI (0.18, 1.65), $P = .28$].

Conclusion: Lycium-rehmannia pills combined with western medicine is better than the control group of therapeutic efficiency in the treatment of dry eye symptom. Due to the quantity and quality limitations of the literature, there were controversial results that the study group was better than the control group in Basic Schirmer test, Tear break up time, Fluorescein test, and reduced adverse reactions, including inflammation of the eyelids and congestion. The above conclusion needs more clinical trials to test and verify.

Abbreviations: CI= confidence interval, MD = mean difference, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RR= risk ratio, SMD = standardized mean difference.

Keywords: dry eye symptom (DES), lycium-rehmannia pills, meta-analysis, randomized controlled trial

1. Introduction

Dry eye symptom (DES), also known as "keratoconjunctivitis sicca," is a general term of various diseases characterized by abnormal tear quality or quantity, or abnormal dynamics of tear film stability, accompanied by discomfort of ocular and/or ocular surface tissue.[1] It is one of the common ophthalmic diseases, and its pathogenic factors are various. Currently, over-reliance on network devices, wear contact lenses for a long time, as well as

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This article is a meta-analysis, which is the secondary processing of data without any restrictions on data access. The quantitative data supporting this META-ANALYSIS are from previously reported studies and datasets, which have been cited. The processed data are available at EndNote X9 and RevMan 5.3.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Department of Pediatrics, [b] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, [c] The Vascular Remodeling and Developmental Defects Research Unit, West China Institute of Women and Children's Health, West China Second University Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Hanmin Liu, Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan, China (e-mail: liuhm@scu.edu.cn).

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after cataract surgery[2] and other reasons are all likely to induce or aggravate DES.[3]

In recent years, the morbidity of DES increased and was demonstrated a younger trend.[4] Currently, its treatment mainly relies on glucocorticoids and nonsteroidal anti-inflammatory drugs, which have certain side effects and tend to cause chronic damage to the eye surface.[5] Therefore, more effective and safe treatments are particularly urgent.[6] With the development of research, traditional Chinese medicine (TCM) treatment methods stand out, and there are many treatments.[7] Among the TCM for treating dry eye, Lycium-rehmannia Pills is the most appreciated herbal formula.[8] DES is regarded as "white astringent syndrome," which is believed to be caused by the deficiency of liver and kidney Yin, the long stagnation of wind heat and fluid deficit and other reasons.[9] Lycium-rehmannia Pills is the formula of chrysanthemum, wolfberry, ripe rehmannia, peony skin, dogwood, yam, alisma, poria cob, etc, which has the effects of nourishing liver and kidney, moistening eyes, promoting fluid production, clearing heat, and brightening eyes.[10] TCM is considered to be a better treatment with fewer side effects. In this study, we applied the evidence-based medicine method to systematically evaluate the clinical randomized controlled trails about Lycium-rehmannia Pills and western medicine for the treatment of DES, the western medicine referred to above be simply the eye drops of western medicine ingredients. Based on objective information on related literature, the meta-analysis results can provide a certain reference basis for clinical application.

2. Methods

This systematic review was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[11] and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[12]

2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria of Lycium-rehmannia Pills for the treatment of dry eye were established according to the standards of Cochrane collaboration.

Inclusion criteria were as follows: Study type: randomized controlled trials were included. All the literature was the full text. Subjects: the included subjects met the diagnostic criteria of the disease in ophthalmology, without any restrictions on gender, race, and nationality. Intervention measures: Lycium-rehmannia Pills combined with western medicine were used in experimental group while simple western medicine was used in the control group. Outcome indicators: including the effective rate and/or adverse reactions (eyelid skin inflammation and congestion).

Exclusion criteria were as follows: duplicate report; research has design defects, cannot extract data; incomplete data, outcome effect is not clear.

2.2. Search strategy

Computer-based retrieval method was applied to search PubMed (October 1966to March 2019), The Cochrane Library (October 1974 to March 2019), EMbase (October 1974 to March 2019), CBM (October 1978 to March 2019), VIP (October 1989 to March 2019), CNKI (October 1994 to March 2019), and Wanfang database. The keywords and subject terms were divided into these parts: xerophthalmia*, dry eye*, dry eye syndrome*, keratoconjunctivitis sicca*, and Lycium-rehmannia pills, lycii and chrysanthemi and rehmanniae bolus*, Lycium-rehmannia wan*, Qiju Dihuang wan*, Qiju Dihuang Pills*. The search words of the randomized controlled trials include randomized controlled trial, random trial, random*, controlled trial*, randomized controlled trial*, randomized controlled trial*, and randomized trial*. All randomized controlled trials (RCT) of Lycium-rehmannia Pills combined with western medicine in the treatment of xerophthalmia were collected, the selection process will be summarized in a PRISMA flow diagram.

2.3. Literature screening, data extraction, and quality evaluation

Two researchers screened literature, extracted data independently, and cross-check-ed the results of included studies according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion with a third person. The absent information was supplemented through contact with authors.

The contents of data extraction table mainly include: Basic information, including title, author, journal, and publication time; Research characteristic, including general conditions of objects in studies, baseline of patients in different groups, and intervention measures; Quality evaluation, according to the Cochrane systematic review member handbook 5. 1. 0 bias risk assessment tool to evaluate the methodological quality of included studies, including random allocation method,[13] allocation concealment, blind implementation, data integrity of results, losing follow-up, quit, reporting bias, and other sources of bias; outcome indicators.

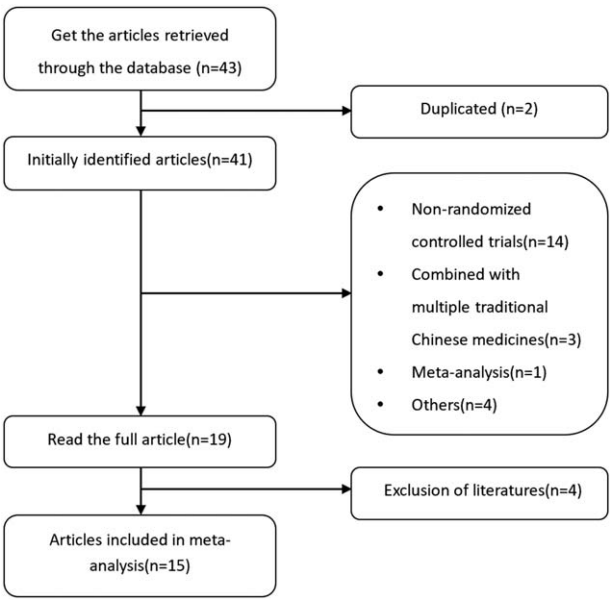

Figure 1. Flow chart of literature search. All patients met the diagnostic criteria for DES and were subjected to randomized controlled trials of Lycium-rehmannia Pills and simple Western medicine, while at least 1 outcome indicator was reported. Diagnosis is unclear, patients are excluded. DES = dry eye symptom.

Table 1

Characteristic and quality evaluation summary of the included studies.

Included literature	Object of study (eyes)		Object of study (n)		Sex ratio (male/female)	Age (control/experimental group)		Course of the treatment (Month)	Intervening measure	Quality evaluation of evidence-based methodology			
	Treatment group	Control group	Treatment group	Control group						Random method	allocation concealment	blind method	Data integrity
Cai X H (2013)	100	100	50	50	43/57	A (45.5±11.0)		1	Lycium-rehmannia Pillwan 8 pill/time, 3 times/d+ Sodium hyaluronate vs Sodium hyaluronate 1 drop/time, 5 times/d	Just the word random	No	No	Yes
Leng Z Y (2018)	50	50	25	25	24/26	A 56.31	A 57.14	3	Lycium-rehmannia Pillwan 8 pills /time, 3 times/d + Polyethylene glycol eye drops vs Polyethylene glycol eye drops, 3 times/d	Just the word random	No	No	Yes
Zhang Z G (2013)	40	36	20	18	12/26	A (44.91±3.22)	A (45.31±2.77)	1	Lycium-rehmannia Pillwan + Sodium hyaluronate vs Sodium hyaluronate 1 drop/time, 5∼6 times/d	Just the word random	No	No	Yes
Tai P C (2018)	62	62	31	31	35/27	A (46.7±3.5)		1	Lycium-rehmannia Pillwan 6 g/time, 2 times/d + Polyethylene glycol eye drops vs Polyethylene glycol eye drops, 1–2 drops/time, 4 times/d	Just the word random	No	No	Yes
Ma H J (2017)	90	90	45	45	43/47	A 28.6	A 25.9	1	Lycium-rehmannia Pillwan 10 pill/times, 3 times/d + Sodium hyaluronate vs Sodium hyaluronate 1∼2drops/time,4times/d	Just the word random	No	No	Yes
Jin G Y (2016)	144	144	72	72	66/78	A (52. 31±8.52)	A (53.16±9.04)	1	Lycium-rehmannia Pillwan 8 pill/time,3 times/d + Sodium hyaluronate vs Sodium hyaluronate, 4 times/d	Random number table	No	No	Yes
Li Q W (2016)	72	72	36	36	41/31	A (50.3±13.5)	A (49.3±15.2)	1	Lycium-rehmannia Pillwan, 9 g/time, 2 times/d + Recombinant fibroblast growth factor gel vs Recombinant fibroblast growth factor gel, 2 times/d	Just the word random	No	No	Yes
Ni C X (2014)	70	70	35	35	46/24	6-15		1	Lycium-rehmannia Pillwan (Dose by age)+ Sodium hyaluronate vs Sodium hyaluronate,1drop/time,3 times/d	Random number table	No	No	No
Zhen W (2014)	50	48	40	40	41/39	A (44.5±2.6)	A (45.7±2.4)	1	Lycium-rehmannia Pillwan, 8 pill/time,3 times/d+ Sodium	Random number table	No	No	Yes

(*continued*)

Table 1

(continued).

Included literature	Object of study (eyes)		Object of study (n)		Sex ratio (male/female)	Age (control/experimental group)		Course of the treatment (Month)	Intervening measure	Quality evaluation of evidence-based methodology			
	Treatment group	Control group	Treatment group	Control group						Random method	allocation concealment	blind method	Data integrity
									hyaluronate vs Sodium hyaluronate, 1 time/d				
Lin Q X (2012)	120	120	60	60	58/62	A 61.2		1	Lycium-rehmannia Pillwan 8 pill/time,3 times/d +Sodium carboxymethyl cellulose sodium drops vs Sodium carboxymethyl cellulose sodium drops,2 times/d	Random number table	No	No	Yes
Ke F J (2011)	80	80	40	40	44/36	A 44.26	A 46.32	1	Lycium-rehmannia Pillwan 1 dose/time, 2 times/d + Dextran and Hypromellose Eye Drops vs Dextran and Hypromellose Eye Drops, 3–6 drops/d	Just the word random	No	No	Yes
Yu Y J (2012)	120	120	60	60	48/72	A (56.86±11.15)	A (54.60±9.45)	1	Lycium-rehmannia Pillwan 9 g/time, 2 times/d+ Sodium carboxymethyl cellulose sodium drops vs Sodium carboxymethyl cellulose sodium drops, 1–2 drops/time, 4 times/d	Random number table	No	No	Yes
Wan J M (2014)	76	76	38	38	40/36	A 45.5	A 42.4	1	Lycium-rehmannia Pillwan 9 g/time, 2 times/d+ Sodium hyaluronate vs Sodium hyaluronate 5–6 times/d	Just the word random	No	No	Yes
Yan K (2014)	40	40	20	20	25/15	A (45.29±4.39)	A (46.01±5.22)	1	Lycium-rehmannia Pillwan 8 pills/time, 3 times/d+ Sodium hyaluronate vs Sodium hyaluronate 1 drop/time, 5 times/d	Just the word random	No	No	Yes
Yung-Hsien Chang (2005)	80	80	40	40	Nu	21–70		2	Chi-Ju-Di-Huan-Wan 4 g/time, 3 times/d+ topical eye drops vs topical eye drops and placebo, 1 drop/time, 4 times/d.	Random number table	Yes	Yes	Yes

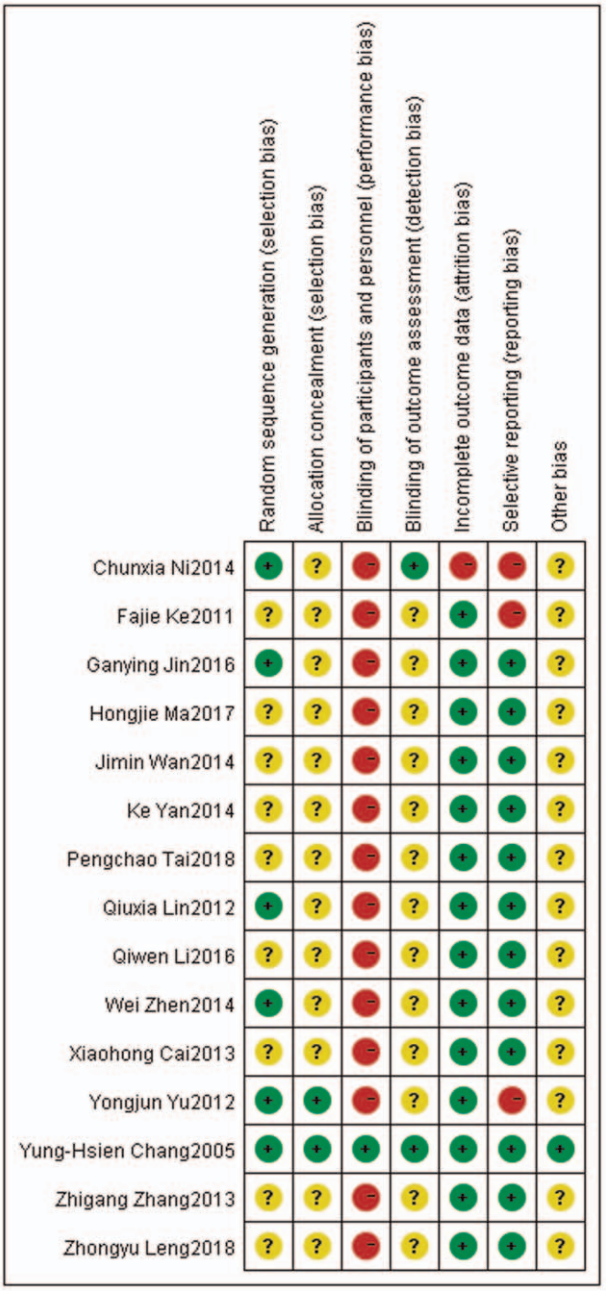

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

2.4. Risk of bias assessment

The methodological quality of each included study was measured independently by 2 authors according to the Cochrane Collaboration's tool.[12] The following contents were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.[12] Each domain was judged to a high level, low level, or unclear level.

2.5. Statistical analysis

The Q statistic test was performed to assess the heterogeneity among studies, I^2 judged the size of heterogeneity, if included study has homogeneity ($P > .1$, $I^2 < 50\%$), the combined analysis will use fixed-effects model, if heterogeneity was significant ($I^2 > 50\%$ and $P < .1$), the cause of heterogeneity should be analyzed to determine whether random effect model can be used. In this study, the relative risk (RR) and 95% confidence interval (CI) were used as the effect scale indicators because the measurement indicators were binary variables.[14] Sensitivity analysis was carried out based on the sample size, the missing data result, and the methodological quality of the included study. If necessary, we will exclude a low-quality study and repeat the meta-analysis to test the stability of the pooled results. A funnel plot will be used to examine the reporting bias. The results will be calcified based on the Cochrane Handbook for Systematic Reviews of Interventions. RevMan 5.3 was applied for Meta-analysis.

3. Results

3.1. Basic information of literature

The selective process of eligible studies for the meta-analysis follows the PRISMA flow diagram. According to the retrieval strategy, 43 related studies were initially found, 1 is in English, the rest in Chinese, 2 of which were re-examined. After reading titles and abstracts, 22 of which were excluded, including 14 nonrandomized controlled trials, 3 of which were combined with multiple traditional Chinese medicines, 1 was meta-analysis, and 4 for other reasons (not case-control). Nineteen RCTs were included in this meta-analysis. Four references were excluded according to read the full text because of additional treatments. Finally, 15 studies were included, all of which were RCT. A total of 1222 patients (eyes = 2382) were included, including 612 in the experimental group and 610 in the control group. The flow chart was shown in Fig. 1.

3.2. Basic characteristics and quality evaluation

Among the 15 included studies,[2,15–28] all of them showed that baseline data between 2 groups were comparable through statistical analysis. 86.67% of the studies reported the specific drug dose,[2,15,17–20,22–28] no detailed dosing was reported in 2 article.[16,21] The average course of treatment was about 1 month, while one 1 literature was about 3 months, accounting for 6.67%,[15] the other was 2 months[28] (6.67%). Besides, 6 articles reported grouping by random number table method (40.00%),[19,21–23,25,28] and the rest only mentioned: "randomly divided into 2 groups." Only one of the included studies referred to the implementation of allocation concealment and blindness.[28] Incomplete data reports and data missing problems existed in 1 study (6.67%),[21] and incomplete data reports were not available in the rest. The basic characteristics and quality evaluation of all included studies are shown in Table 1. The Cochrane risk bias assessment of the quality of the article was shown in Figs. 2 and 3.

3.3. Meta-analysis

3.3.1. Therapeutic efficiency. There is a literature on the therapeutic efficiency of treatment not mentioned, a total of 1142 patients were included in 14 RCT studies, including 572 patients in the experimental group with a total of 1114 eyes, and 570

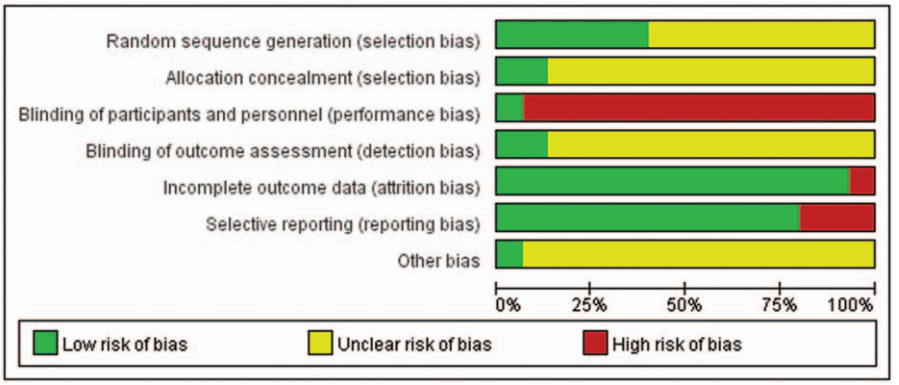

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

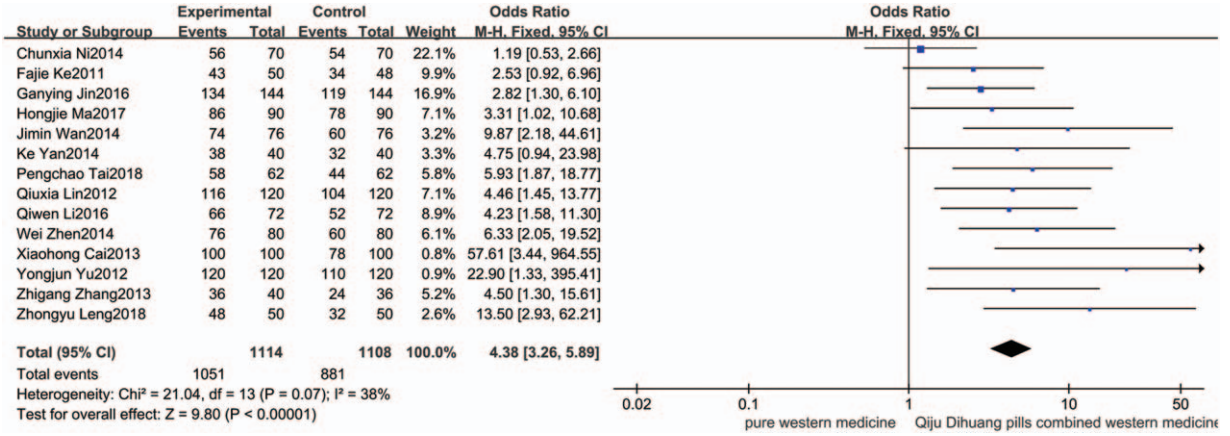

Figure 4. The meta-analysis results of the therapeutic efficiency of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. There are 1142 patients who were included in 14 RCT studies, including 572 patients in the experimental group with a total of 1114 eyes, and 570 patients in the control group with a total of 1108 eyes. RCTs = randomized controlled trials.

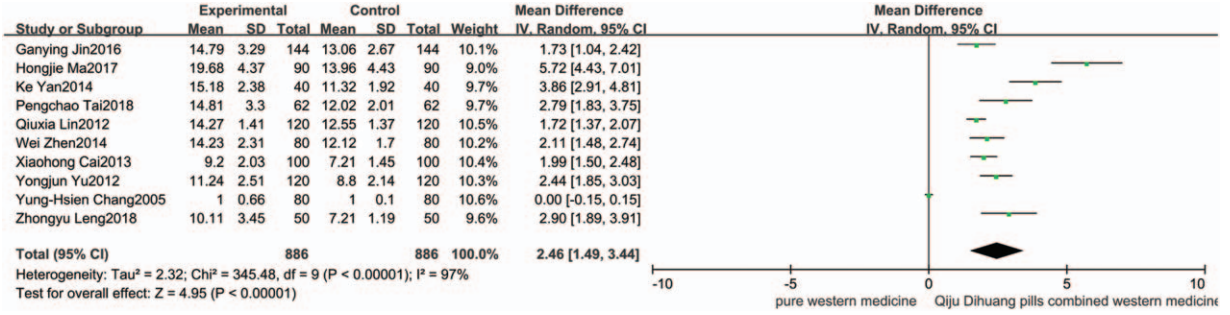

Figure 5. The meta-analysis results of the Basic Schirmer test of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. Basic Schirmer test was evaluated in 10 articles, involving a total of 886 patients with a total of 1772 eyes.

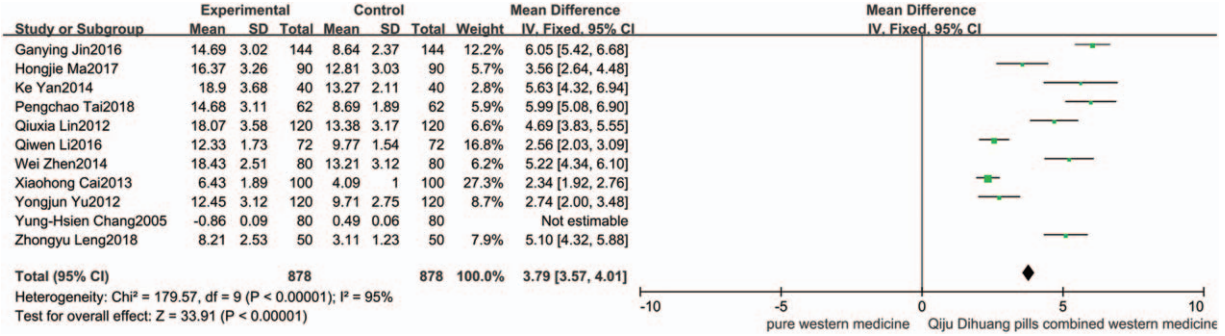

Figure 6. The meta-analysis results of the Tear break up time (BUT) of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. BUT was assessed in 11 studies, involving a total of 958 patients with a total of 1916 eyes.

patients in the control group with a total of 1108 eyes. It was shown that there was no statistical significance between the groups by the heterogeneity test [$I^2 = 38\%$]. The fixed-effect model was used to perform a meta-analysis. The result has shown that there was a statistically significant difference in the effective rate of Lycium-rehmannia pills combined with western medicine compared with western medicine alone in the treatment of dry eye [OR = 4.38, 95% CI (3.26, 5.89), $P < .00001$]. The corresponding forest plot was shown in Fig. 4.

3.4. Basic Schirmer test

Basic Schirmer test was evaluated in 10 articles, involving a total of 886 patients with a total of 1772 eyes. Meta-analysis results showed that there was heterogeneity among these studies ($P < .00001$, $I^2 = 97\%$). The random-effect model was applied to perform the meta-analysis. The subgroup analysis was conducted based on the subject age, gender ratio of subjects, and publishing year of articles to analyze the source of heterogeneity. Unfortunately, we did not find the source of heterogeneity. The results that the patients treated by Lycium-rehmannia pills combined with western medicine had a higher Schirmer than the control [MD, 2.46, 95% CI (1.49, 3.44), $P < .00001$] in the treatment of dry eye symptom need to be verified by more studies, as shown in Fig. 5.

3.5. Tear break up time (BUT)

Tear break up time (BUT) was assessed in 11 studies, involving a total of 958 patients with a total of 1916 eyes. Due to the extremely high heterogeneity, the random-effect model should be used. One of the studies was heavily weighed in the random effects model, so sensitivity analysis was applied to eliminate the study. After the literature was excluded, subgroup analysis is still needed to study the sources of heterogeneity; however, the results are still inconclusive. According to the BUT, there was a controversial result that the study group was better than the control group [MD, 3.79, 95% CI (3.57, 4.01), $P < .00001$], as shown in Fig. 6.

3.6. Fluorescein test

Five relevant studies applied Fluorescein test. Due to heterogeneity between studies ($P < .00001$, $I^2 = 97\%$), the random-effect model was selected. However, the result could not provide the certain conclusion. The results showed that Lycium-rehmannia pills combined with western medicine could not reduce fluorescein staining of the cornea compared with the control group [MD, −1.29, 95% CI (−1.42, −1.15), $P < .00001$], as shown in Fig. 7.

3.7. Clinical adverse reaction—eyelid dermatitis

There were 7 RCT studies on eyelid skin inflammation, including 248 cases of the experimental group and 248 cases of the control group. The results of the fixed-effect model meta-analysis showed that Lycium-rehmannia pills combined with western medicine could not better reduce the incidence of adverse reactions to eyelid skin inflammation compared with the control

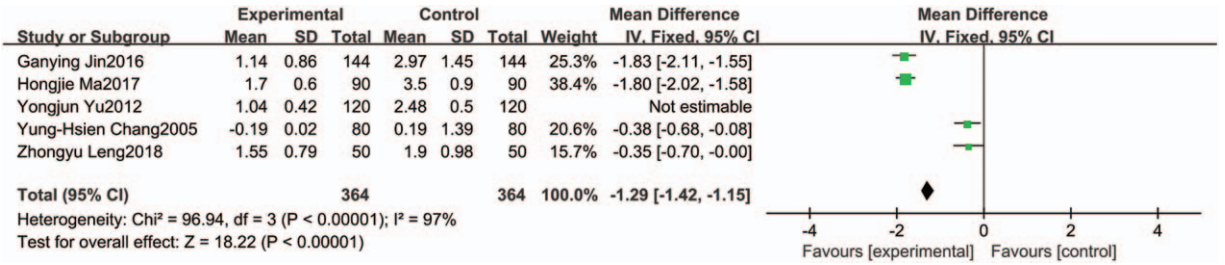

Figure 7. The meta-analysis results of the Fluorescent test of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. Five relevant studies applied Fluorescein test.

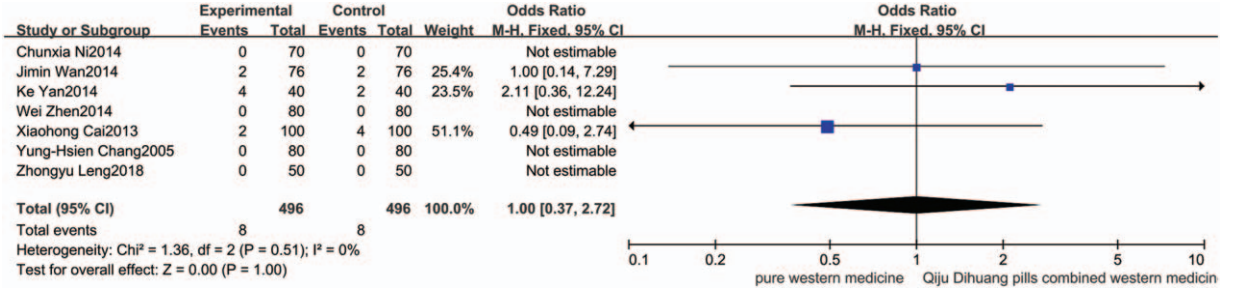

Figure 8. The meta-analysis results of the incidence of the adverse reactions (eyelid skin inflammation) of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. There were 7 RCT studies on eyelid skin inflammation, including 248 cases of the experimental group and 248 cases of the control group.

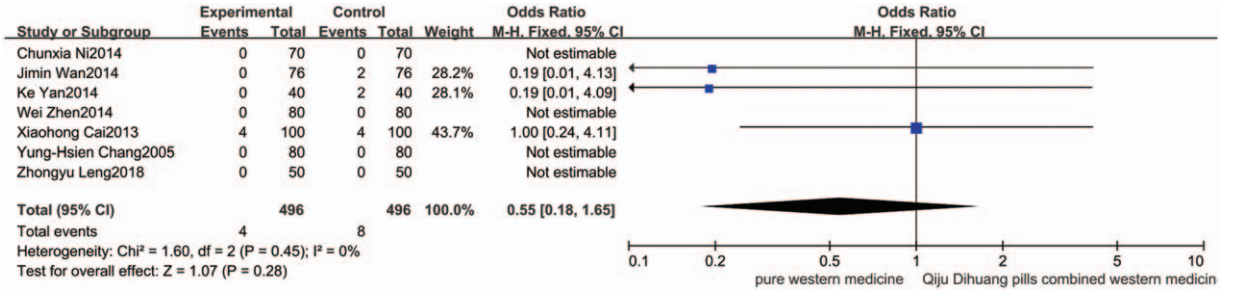

Figure 9. The meta-analysis results of the incidence of the adverse reactions (hyperemia) of Lycium-rehmannia pills combined with western medicine in the treatment of dry eye. Seven RCT studies were included, including 248 cases (eyes = 496) in the experimental group and 248 cases of the control group.

group [OR = 1.00, 95% CI (0.37, 2.72), $P = 1.00$]. The result was shown in Fig. 8.

3.8. Adverse clinical reactions—hyperemia

Seven RCT studies were included, including 248 cases (eyes = 496) in the experimental group and 248 cases of the control group. Meta-analysis results of fixed effect model showed that: compared with western medicine alone, Lycium-rehmannia pills combined with western medicine could not reduce the incidence of ADR congestion in the treatment of Dry eye syndrome [OR = 0.55, 95% CI (0.18, 1.65), $P = .28$]. The result was shown in Fig. 9.

3.9. Evaluation of publication bias

To assess the risk of publication bias, efficient funnel plot analysis was carried out for 14 included studies (Fig. 10). It was found that the funnel plot presented a skewed distribution and 1 point fell outside the funnel plot, which indicated that there might be some publication bias in the data.

4. Discussion

In Traditional Chinese medicine, DES is regarded as "white astringent," "Shen Shui will dry," and "dryness syndrome." The cause of the disease is complex, and there is no special treatment method, and traditional Chinese medicine is expected to be the preferred method for treating dry eye disease.[29]

In this paper, we applied the meta-analysis method to evaluate the improvement on therapeutic effect and reducing adverse reactions to the Lycium-rehmannia pills in the treatment of dry eye symptom. The results showed that the study group revealed more improvement than the control group in total effective rate. It could not effectively reduce adverse reactions (eyelid skin inflammation and congestion), however, due to the incompleteness of the outcome index and the limitation of the follow-up time, the result needs further study. And more high-quality studies are needed to verify effects in Basic Schirmer test, Tear BUT, and Fluorescein test.

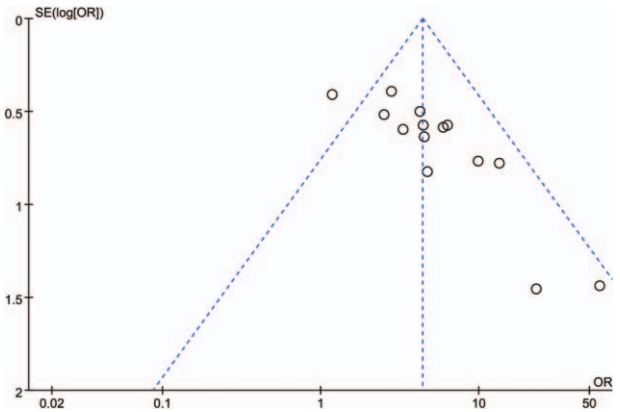

Figure 10. The funnel plot about the total efficiency.

At the same time, many included studies are of low quality. There is a limited amount of data, and all of them are acquired in China. In the case of random control test design, there is no detailed explanation of the random method, and most of the literature does not mention the implementation of blind method and the hidden grouping, and several articles have incomplete reports, so they are easy to lead to random bias, implementation bias, and measurement bias, which all have a certain degree of influence on the research results. In the adverse reactions, the lack of objective and detailed adverse reactions causes a certain problem and influences on the final results. Also, the lack of long-term effect and the recurrence of the patient cause some limitations on the judgment. The future of the case of dry eye disease should be noted in the following aspects: The method is designed strictly by the randomized controlled test, and the risk of bias is reduced; To improve the outcome indicators and report the occurrence of adverse reactions; The clinical effect is as close to the actual situation as possible.

In summary, Lycium-rehmannia pills were significantly improved eye symptoms, but the difference in the incidence of adverse reactions is not statistically significant, and the meta-analysis provides a reflection and enlightenment for the clinical treatment of dry eye disease. As the insufficient high-quality RCTs and publication bias, it still needs to be further verified by large, high-quality, and multicenter RCT.

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Author contributions

Conceptualization: Lili Lou.
Data curation: Lili Lou, Hongling Fu.
Formal analysis: Lili Lou.
Investigation: Lili Lou.
Methodology: Lili Lou, Hongling Fu.
Project administration: Lili Lou.
Resources: Lili Lou.
Software: Lili Lou, Hongling Fu.
Supervision: Hanmin Liu.
Validation: Lili Lou, Hongling Fu.
Visualization: Lili Lou.
Writing – original draft: Lili Lou.
Writing – review & editing: Lili Lou, Hongling Fu, Hanmin Liu.

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