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Systematic Review

Acupuncture for dry eye syndrome: a meta-analysis of randomized controlled trials

针刺治疗干眼症的 Meta 分析

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Abstract
Objective: To summarize and critically assess the evidence from randomized controlled trials (RCTs) of acupuncture in treating dry eye syndrome (DES) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Collaboration recommendations.
Methods: A search of PubMed, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and Embase was made from their inception to August 2016, as well as Chinese, Japanese, and Korean databases. Two reviewers independently selected RCTs and assessed the methodological quality. Meta-analysis and the level of evidence were processed by RevMan 5.3 and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
Results: After selection, 8 trials were subjected to our systematic review. The methodological quality was low generally. The 3-10 weeks follow-up showed that acupuncture improved the tear film break-up time (BUT) (MD=1.33, 95% CI=1.01-1.66, 619 participants). The mean difference of Schirmer's test was 1.73 mm (95%CI=1.28-2.18, 618 participants) between the acupuncture group and the control group. The subjective variables exhibited no significant differences.
Conclusion: The low methodological quality of the trials does not suggest drawing firm conclusions on the value of acupuncture therapy for DES. Acupuncture treatment may have some effects on the tear film BUT and Schirmer's test, but not on the subjective symptoms. Well-planned large-scale high-quality RCTs are needed to make it clear whether acupuncture is effective in treating DES.
Keywords: Acupuncture Therapy; Dry Eye Syndrome; Randomized Controlled Trial; Systematic Review; Meta-analysis

【摘要】目的：根据系统综述和 meta 分析优先报告的条目(PRISMA)声明和 Cochrane 协作中心推荐的方法，严格评估和总结针刺治疗干眼症的随机对照试验的结果。**方法**：检索 PubMed, Cochrane 临床试验注册中心，ClinicalTrials.gov 和 Embase，以及中文、日文和韩文数据库，从建库时间到 2016 年 8 月。两位研究人员分别筛选 RCTs 并评估其方法学质量。采用 Revman5.3 和 GRADE 进行 Meta 分析和证据分级。**结果**：本系统评价共纳入 8 项试验，其方法学质量普遍偏低。随访 3-10 星期，与对照组相比，针刺治疗可以改善泪膜破裂时间(BUT, MD＝1.33, 95% CI＝1.01-1.66, 619 例)。针刺组和对照组之间 Schirmer's 试验的差值为 1.73 mm (95% CI＝1.28-2.18, 618 例)。其他主观结局指标两组间无显著差异。**结论**:由于目前纳入的临床试验方法学质量较低，尚不能得出针刺治疗干眼症疗效的确切结论。针刺疗法可能对 BUT 和 Schirmer's 试验有一定影响，但是对主观症状无明显作用。设计严谨的大规模高质量随机对照试验将有助于明确针刺治疗干眼症的临床疗效。
【关键词】针刺疗法；干眼症；随机对照临床试验；系统评价; meta 分析
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Dry eye syndrome (DES) is one of the most common and irritating opthalmological problems worldwide. Its prevalence is estimated to be in the range of 5% to 35% and its incidence has been increasing[1], more rapidly than other ophthalmologic diseases such as cataracts, retinal disease and glaucoma[2]. Dry eye may bring problems with reading, carrying out professional work, using computer, watching television, driving[3], and even cause limitations in the activities of daily life, bodily pain, discomfort and lower energy and vitality[4].

The conventional treatment is mostly artificial tears[5]. Meanwhile, patients with eye diseases often turn to complementary and alternative medicine[6]. Acupuncture is a widely used treatment modality for

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various conditions, including ophthalmologic diseases[7]. The efficacy of acupuncture for DES has also been studied: recent studies[8-9] have suggested that acupuncture should be helpful for it, but other studies[10-11] failed to reach a consensus that acupuncture treatment is the most effective therapy.

Therefore, the objective of this systematic review was to summarize and critically assess the evidence from randomized clinical trials (RCTs) of acupuncture in treating DES according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Collaboration recommendations[12-13].

1 Methods

1.1 Inclusion criteria

1.1.1 Study types

RCTs of acupuncture in treating DES using acupuncture with or without electrical stimulation as sole or adjunctive treatment.

1.1.2 Participants

We included studies conducted in adults (age over 18 years old), with dry eye defined by the study investigators with no restrictions on race or sex.

1.1.3 Interventions

Acupuncture was defined as the insertion of needles into skin and underlying tissues at particular sites for therapeutic or preventive purposes. Trials that tested other forms of acupuncture (no needle insertion), such as laser acupuncture, transcutaneous electrical nerve stimulation, and moxibustion, were excluded. Trials with designs that did not allow an evaluation of effectiveness of acupuncture (e.g. using treatments of unproven effectiveness in the control group or comparing 2 different forms of acupuncture) were excluded. Studies combining 2 different forms of acupuncture in the experimental group were also excluded. Trials published in the forms of dissertation and abstract were included. No language restrictions were imposed.

1.1.4 Outcome measures

Clinical tests for dry eye generally do not correlate with participant-reported symptoms. There are a wide variety of participant-reported outcome scales that actually lead to the discrepancies between subjective symptoms and objective clinical tests[13-14]. Therefore we took into consideration both subjective data from participant-reported symptoms regardless of measurement scale and objective data obtained from clinical diagnostic tests to fully analyze the effect.

Tear film break-up time (BUT) and Schirmer's test results were obtained and recorded[15].

1.2 Search strategy

1.2.1 Electronic search

The following electronic databases were searched from their inception dates to August 2016: PubMed, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Korean medical databases, China National Knowledge Infrastructure (CNKI), Chongqing VIP Database (CQVIP), Wanfang Academic Journal Full-text Database (Wanfang), and Japanese databases. As the involved databases all possessed their own subject headings, each database was searched independently. Key words used for search were (dry eye OR xerophthalmia OR keratoconjunctivitis sicca) AND (acupuncture OR puncture OR needle OR needling). No language restrictions were imposed.

1.2.2 Other search resources

To reduce publication bias, both unpublished and published articles, and abstracts were eligible for inclusion. The references for all the targeted articles, including other systematic reviews were searched manually. We tried to contact the corresponding authors of the articles via e-mail to ask if there were any new results.

1.3 Data collection and analysis

1.3.1 Selection of studies

The selection of studies for inclusion was carried out by two authors (Jiang Hui-ru and Liu Su-jun) independently. They screened the abstracts for all identified potential studies. All articles with possible relevance were then retrieved in full text for comprehensive assessment; disagreement was resolved by discussion or consensus with a third author (Zhang Bi-meng).

1.3.2 Data extraction and management

The information was extracted independently by two reviewers (Liu Peng and Liu Su-jun). All study characteristics and outcome data were independently conducted according to predefined criteria using standard data extraction forms; disagreement was resolved by discussion or consensus with a third author (Jiang Hui-ru). Duplicate publications, missing data, changes in data, median data, and standard deviation were dealt by methods from the Cochrane Handbook[13].

1.3.3 Assessment of bias risk in the included studies

Risk of bias was independently assessed by two reviewers (Liu Peng and Liu Su-jun) using Cochrane tool[13]. Agreement for study selection was based on the result of the quadratically weighted Kappa statistic (Kw). Only when the Kw was over 0.75, we could use the result, and disagreements were resolved by consensus with additional two authors (Jiang Hui-ru and Zhang Bi-meng).

1.3.4 Measures of treatment effects

For the direct Meta-analysis, mean differences of continuous outcomes (e.g. pain, disability) were pooled using weighted mean differences. If it was not possible, the standardized mean differences were used with different scales[13].

Meta-analysis and the level of evidence were performed by Revman 5.3 and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We compared the final results to assess differences between the intervention and control groups. Cochrane's Chi-square test and I^2 were used to assess the heterogeneity, which was assumed if the *P*-value was less than 0.10. If the I^2 value was above 75%, the heterogeneity was high[13]. Clinical heterogeneity was assessed by noting the differences in the distribution of participants' characteristics among trials (e.g. age, duration of disorder and associated diseases). Clinically and statistically homogeneous studies were pooled using the fixed effect model. Clinically homogeneous and statistically heterogeneous studies were pooled using the random effects model.

1.3.5 Assessment of reporting biases

Funnel plots were generated if sufficient trials were available to assess the publication bias and other related biases, at least 12[16].

1.3.6 Qualitative analysis

Two reviewers (Jiang Hui-ru and Liu Su-jun) independently evaluated the quality of the evidence using the GRADE approach[17], and disagreements were resolved by consensus with a third author (Zhang Bi-meng). We assessed the quality of domains that may downgrade the quality of the evidence such as: a. risk of bias; b. inconsistency; c. indirectness; d. imprecision; e. publication bias. Domains that may upgrade the quality of the evidence were a. large-effect; b. plausible confounding would have changed the effect; c. dose-response gradient. The quality of the evidence would be described as high, moderate, low and very low.

2 Results

2.1 Description of studies

The exclusion was first performed by screening the titles and abstracts, including 98 duplicates. The full-text articles of the remaining 19 studies were retrieved for additional scrutiny, of which, 6 were proved ineligible because of no mention of randomization or quasi-randomization. There were 3 ongoing studies that had no recent results (ClinicalTrials.gov Identifier: NCT00554879, NCT02219204, and a protocol)[18]. After selection, 8 trials were finally subjected to our systematic review[8,19-25], and 1 trial had been registered in the ClinicalTrials.gov[19]. Among the 8 publications, the types of control interventions and data extraction are depicted in Table 1. Five trials took artificial tear as the control[8,19-22]. In two studies, patients were given acupuncture in addition to the active treatment[23-24]. Six trials were based in China, and one in the South Korea.

2.2 Risk of bias of the included studies

A graphical summary of the risk of bias assessments of the included studies was made based on the risk of bias domains (Figure 1). The Kw of two methodological quality reviewers (Liu Peng and Liu Su-jun) was over 0.82.

Table 1. Summary of RCTs of acupuncture for dry eye

Trial	Group	*n*	Female/male	Age (year)	Duration	Treatment methods	Treatment course
Kim TH 2012[19]	Treatment	75	53/22	47.95±11.11	(6.00±5.69) years	Acupuncture [Cuanzhu (BL 2), Yangbai (GB 14), Sizhukong (TE 23), Sishencong (EX-HN 1), Chengqi (ST 1), Fengchi (GB 20), Hegu (LI 4), Quchi (LI 11), Shangxing (GV 23)]	4 weeks
	Control	75	56/19	46.05±13.10	(5.91±4.97) years	Artificial tear	4 weeks
Zhang Y 2007[20]	Treatment	30	19/11	22-64	3 months-4 years	Acupuncture [Baihui (GV 20), Jingming (BL 1), Cuanzhu (BL 2), Taiyang (EX-HN 5), Sibai (ST 2), Fengchi (GB 20), Hegu (LI 4), Zusanli (ST 36), Sanyinjiao (SP 6), Taixi (KI 3), Taichong (LR 3)]	40 d
	Control	31	18/13	20-66	2 months-5 years	Artificial tear	40 d
Shi JL 2012[8]	Treatment	33	19/14	26-63	Not available	Acupuncture [Baihui (GV 20), Jingming (BL 1), Chengqi (ST 1), Taiyang (EX-HN 5), Sizhukong (TE 23), Hegu (LI 4), Zusanli (ST 36)]	3 weeks
	Control	35	19/16	27-65	Not available	Artificial tear	3 weeks

Table 1. Summary of RCTs of acupuncture for dry eye: continue

Trial	Group	*n*	Female/male	Age (year)	Duration	Treatment methods	Treatment course
Wang ZL 2005[21]	Treatment	15	8/7	27-75	6 months-10 years	Acupuncture [Quchi (LI 11), Yingxiang (LI 20), Sibai (ST 2), Xuehai (SP 10), Hegu (LI 4), Zusanli (ST 36), Sanyinjiao (SP 6), Taixi (KI 3), Cuanzhu (BL 2), Sizhukong (TE 23), Chengqi (ST 1), Yangbai (GB 14)]	30 d
	Control	15	10/5	30-73	2 months-10 years	Artificial tear	30 d
Wei LX 2010[22]	Treatment	40	30/10	44.75 ± 17.06	(30.18±31.69) months	Acupuncture [Baihui (GV 20), Jingming (BL 1), Cuanzhu (BL 2), Taiyang (EX-HN 5), Sibai (ST 2), Shenting (GV 24), Hegu (LI 4), Zusanli (ST 36), Sanyinjiao (SP 6), Taixi (KI 3), Taichong (LR 3)]	40 d
	Control	40	27/13	42.98 ±12.54	(30.20±43.76) months	Sodium hyaluronate eye drops	40 d
Tseng KL 2006[23]	Treatment	17	11/6	47.58 ±14.88	(3.24 ±3.17) years	Acupuncture [Taiyang (EX-HN 5), Sizhukong (TE 23), Yangbai (GB 14), Sibai (ST 2), Sanyinjiao (SP 6)]	8 weeks
	Control	9	3/6	51.33 ± 20.91	(4.00±3.35) years	Artificial tears	8 weeks
Li K 2013[24]	Treatment	169	132/37	19-69	Not available	Acupuncture [Jingming (BL 1), Cuanzhu (BL 2), Sizhukong (TE 23), Tongziliao (GB 1), Taiyang (EX-HN 5), Hegu (LI 4)]	8 weeks
	Control	170	122/48	19-69	Not available	*Run Mu Ling*	8 weeks
Ni W 2016[25]	Treatment 1	30	17/13	32±8	(12±7) months	Acupuncture [Jingming (BL 1), Sanyinjiao (SP 6), Taixi (KI 3), Shuigou (GV 26), Qiuhou (EX-HN 7)]	3 weeks
	Treatment 2	32	17/15	36±7	(11±6) months	Acupuncture [Jingming (BL 1), Sanyinjiao (SP 6), Taixi (KI 3), Qiuhou (EX-HN 7)]	3 weeks
	Control	31	23/8	32±10	(14±9) months	Hyaluronic acid sodium eye drops	3 weeks

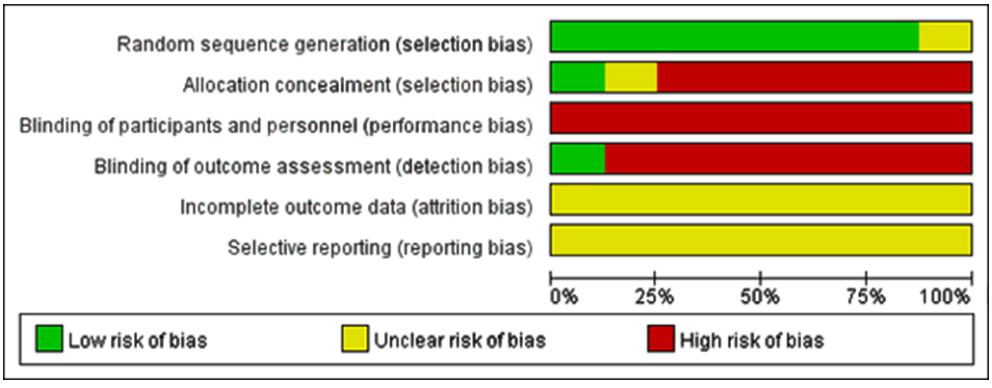

Figure 1. Risk of bias of the included studies

The methodological quality of the included trials varied substantially and was low generally (Figure 1 and Figure 2). No trial was at a low risk of bias in all domains. Most of these trials reported using a randomization method, but only 1 of these offered an adequate description of allocation concealment. We found that all of the studies fell short of the blinding procedures for both patients and care providers, and only 1 of the 8 publications reported assessor blinding. Because of the specific characteristics of acupuncture therapy, it's hard to blind the patient, and impossible to blind the care provider in acupuncture treatment. The groups of most trials were similar at baseline regarding the most important prognostic indicator and the timing of the outcome assessment, but the comparability of co-intervention and compliance were always neglected.

2.3 Effects of interventions

The 8 publications all reported BUT and Schirmer's test outcomes. At 3-10 weeks follow-up, acupuncture improved BUT more significantly [MD 1.33, 95% CI＝1.01-1.66, 619 participants, Figure 3] compared with active treatment (artificial tear or Sodium hyaluronate eye drops). The mean difference of Schirmer's test was 1.73 mm (95% CI＝1.28-2.18, 618 participants, Figure 4) between the acupuncture group and active treatment (artificial tear or Sodium hyaluronate eye drops).

Subjective variables exhibited significant differences in two studies[21,24]. Changes in ocular surface disease index (OSDI) did not show significant differences between the two groups[19,22]. In terms of the number of applications of artificial tears, the mean score of frequency of eye-drop use had no statistically significant difference between the groups[23].

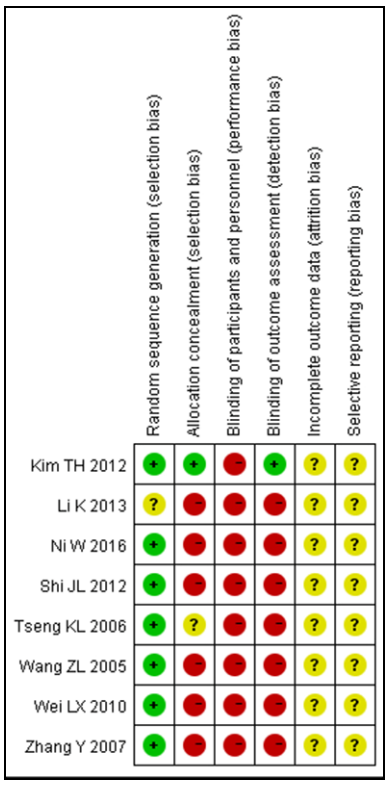

Figure 2. Risk of bias of each included trial

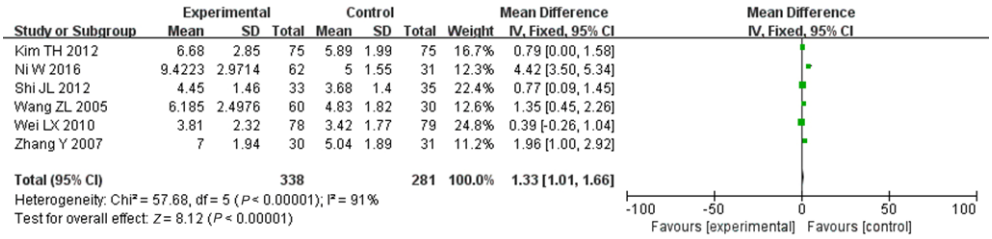

Figure 3. Effect of acupuncture on BUT in DES

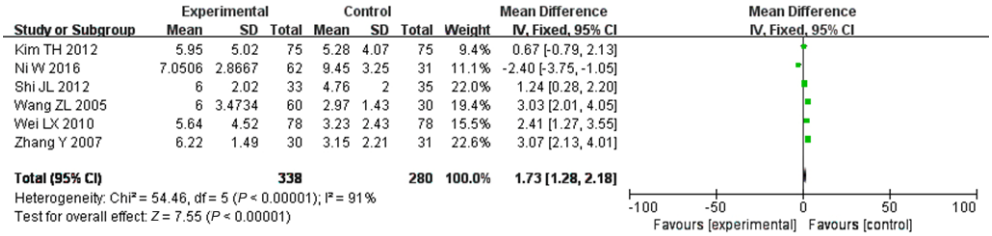

Figure 4. Effect of acupuncture on Schirmer's test in DES

3 Discussion

3.1 Summary of evidences

Our aim in performing this systematic review was to analyze the highest quality evidence from RCTs to determine the efficacy of acupuncture in treating people with DES. However, the majority of the published literatures are limited in methodological quality. We identified eight RCTs that investigated the effects of acupuncture compared to artificial tears[8,19-25].

Based on the reported data from the included studies, acupuncture was associated with a significant improvement in aqueous tear production as measured by Schirmer's test (very low quality evidence). Regarding tear film stability as measured by tear BUT, a statistically, but not clinically, meaningful difference was showed between acupuncture and artificial tears for dry eye participants after several weeks of treatment (very low quality evidence). Acupuncture treatment could not improve the subjective symptoms (very low quality evidence).

Although precise measurement of symptoms is an important part of dry eye diagnosis, there is no universally accepted standardized method for recording participant-reported symptoms; it is commonly observed that participant-reported symptoms do not correlate with objective clinical tests[26-27]. In this review, each study applied different methods to measure participant-reported symptoms. Taking into consideration the wide array of subjective questionnaires and scales used to measure participant symptoms and differences in the length of follow-up, improvement in participant-reported symptoms was not consistently observed in the eight trials.

3.2 Evidence quality

The assessment of overall risk of bias showed a high risk in most studies, suggesting an absence of high level of evidence. The included RCTs lack randomization and blinding methods, leading to higher risk of bias and low level of evidence in conclusions.

3.3 Potential biases in the review process

Bias can be introduced in many ways in the process of locating and selecting studies for inclusion in a meta-analysis. Although our literature searches included English, Chinese, Korean and Japanese data bases, we can't be sure that all relevant trials had been found. Moreover, selective publishing and reporting is another major cause of bias that must be considered[28]. Many trials had a small sample size and the heterogeneity may make it underpowered to detect the benefit of acupuncture therapy. Meta-analyses of small trials have been shown to be potentially unreliable in other medical areas, and we should not ignore these facts[29-30]. A major difficulty in summarizing results from the included studies was the heterogeneity in the participants, interventions and comparisons, as well as variations in the procedures of acupuncture treatment.

Future studies must have a random sequence generation protocol as well as appropriate concealment of the treatment assignments before allocation, and should be stratified by age and severity of dry eye. And also, future studies should make attempts to ensure both participants and study investigators (clinical staff and outcome assessors) are blind to the treatment assignments in order to limit potential bias in participant-reported outcomes. Any future studies should utilize standardized and validated scoring systems of dry eye clinical severity and symptom questionnaires. Objective biomarkers, which have been reported as a parallel index of the dry eye severity scale, such as tear osmolarity and cytokines[31-32], should be applied as a part of the outcomes. Analyses should include both short-term (2 to 4 weeks) and long-term (6 to 12 months) outcomes.

3.4 Conclusion

The low methodological quality of the trials does not suggest drawing firm conclusion on the value of acupuncture therapy for dry eye. Acupuncture treatment may have some effect on tear BUT and Schirmer's test, but not on the subjective symptoms. Well-planned, large scale, high-quality randomized controlled trials are needed.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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