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Review Article

Therapeutic effects of acupuncture in typical dry eye: a systematic review and meta-analysis

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ABSTRACT.
Acupuncture is a treatment option for dry eye syndrome (DES), but its efficacy remains still controversial. We assessed the effectiveness of this treatment for typical DES without specific aetiologies. Eight databases up through June 2018 were searched for randomized clinical trials (RCTs) comparing treatments of acupuncture with artificial tears. The risk of bias was assessed using Cochrane criteria, and a random effects model was used for meta-analyses on tear-film breakup time (BUT), Schirmer test, corneal fluorescein staining (CFS), ocular surface disease index, visual analogue scale and score of symptoms (SOS). Subgroup and sensitivity analyses were conducted to explore the heterogeneity, and publication bias was assessed by funnel plot using Egger's test. Twenty-one RCTs in 19 studies (*n* = 1542 eyes) met our eligible criteria. The results demonstrated the superiority of acupuncture in improving the symptoms of BUT, Schirmer test, CFS and SOS, compared to artificial tears acting alone. The BUT and Schirmer test were also more improved in acupuncture combination with artificial tears than artificial tears alone. Further subgroup analyses suggest that acupuncture applied at 2.0–3.0 times per week for 21–30 days may be optimal for treating typical DES. This provides useful information for guiding acupuncture in the clinical trials.

Key words: acupuncture protocol – artificial tear – keratoconjunctivitis sicca – Schirmer – tear-film breakup time

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Introduction

Dry eye syndrome (DES) is a multifactorial eye disease affecting 14% to 33% of the population worldwide (Pflugfelder 2008). The aetiology includes tear-film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities (Bron et al. 2017). The altered tear-film leads to symptoms of ocular dryness, irritation, itching, a burning sensation and congestion, which impair quality of life (Bhavsar et al. 2011). Dry eye syndrome (DES) is pathologically classified into two major subtypes, aqueous-deficient and evaporative dry eye (Bron et al. 2017). Among the aqueous-deficient dry eye without specific causes, especially Sjögren's syndrome, the most common form is age-related DES. The incidence of non-specific typical DES is currently climbing due to increased exposure to video terminals, enclosed air-conditioned environments, contact lenses and refractive surgery, along with growth of the ageing population (Pflugfelder 2008). The main management for treating DES is a drop of artificial tears as a lubricant for tear deficiency (Bhavsar et al. 2011). The supplementation relieves the symptoms by diluting inflammatory mediators and reducing the tear-film hyperosmolarity and stress, but the temporary efficacy lasting only 30–40 min requires the frequent applications. Although the artificial tears containing anti-inflammatory agents and autologous serum tears have been developed, the patients who are dissatisfied with the treatments seek other remedies reported as being effective, leading to emerging interest in complementary and alternative medicines.

Acupuncture, as a component of Traditional Chinese Medicine for several thousands of years, employs fine needles to target specific points on the body, known as acupoints, which is a major intervention for a variety of disorders in eastern Asia (Sierpina & Frenkel 2005). The World Health Organization lists ophthalmic disorders for which acupuncture can be effective, including acute conjunctivitis, central retinitis, myopia and cataracts (Stux et al. 2012). While acupuncture also has been reported as effective in other ophthalmic disorders including DES (Law & Li 2007; Liu et al. 2009; Lee et al. 2011), its efficacy on DES remains controversial due to inconsistent data (List et al. 1998; Gronlund et al. 2004; Jeon et al. 2010; Shin et al. 2010; Shi & Miao 2012). This suggests a growing need for evidence-based studies to assess its effectiveness. Systematic reviews and meta-analyses provide currently evidences that acupuncture improves the symptoms of DES more than artificial tears (Lee et al. 2011; Ba et al. 2013; Yang et al. 2015; Jiang et al., 2017a; Kim et al. 2018). However, the randomized controlled trials (RCTs) included are not sufficient to conclude the effectiveness. The meta-analysis actually has some difficulties in obtaining datasets and the processing, because the RCTs are a few and mostly written in Chinese. Further, the RCTs include patients with DES regardless of the aetiology, and the acupuncture protocols vary widely. This indicates the need to establish the effectiveness of acupuncture treatment based on the differential aetiology of DES.

Therefore, we conducted meta-analyses to evaluate the effectiveness of acupuncture (AC) and its combination with artificial tears (AC + aT) on typical DES (without Sjögren's syndrome or other specific causes) as compared with artificial tears alone (aT). The effects were assessed by clinical tests and patient-reported symptom measures: clinical tests include tear-film breakup time (BUT) for tear-film instability, Schirmer test for tearing and corneal fluorescein staining (CFS) for lubricating. Patient-reported symptom measures as self-assessments using questionnaires include the ocular surface disease index (OSDI) and the visual analogue scale (VAS) of ocular discomfort, and the score of symptoms (SOS) following treatments (DEWS 2007).

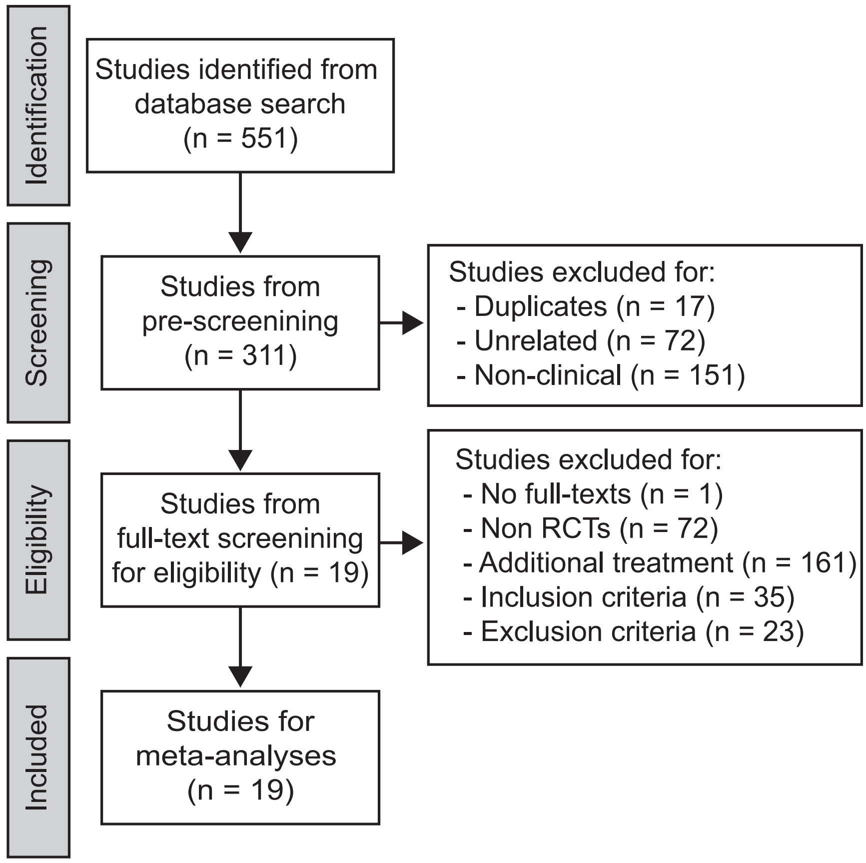


Fig. 1. Flow diagram for study selection. RCT: randomized controlled trial.

Methods

Literature search strategy

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1) (Liberati et al. 2009). Eight electronic databases of PubMed, Medline, Web of Science, Cochrane, China National Knowledge Infrastructure, Wangfang, Oriental Medicine Advanced Searching Integrated System and Research Information Sharing Service were searched from their inception to June 2018. There were no language restrictions. The first search keywords were "acupuncture" with "dry eye", "xerophthalmia" or "keratoconjunctivitis sicca", and the second keywords were "treatment", "alternative medicine" or "complementary medicine" as extended search terms. The reference lists of the relevant studies and reviews were also checked to identify other potentially eligible studies.

Study selection and eligibility criteria

Study selection was performed independently by three reviewers (N.J.H., J.J.H. and P.J.G.). Screening and reviewing included removing duplications, title and abstract screening and full-text review. Articles which cannot access to the full-text were excluded. The screened studies were included according to the following eligibility criteria: (1) acupuncture trials in adult patients with DES, but with no restrictions on age, race, gender or disease duration and severity; (2) trials through the insertion of needles at acupoints; (3) trials with a study design of acupuncture or its combination with artificial tears versus a control group with aT alone; and (4) trials including outcomes from two main clinical tests of BUT and Schirmer tests at least. Studies excluded were as follows: (1) trials in patients with DES caused by systemic diseases (e.g. Sjögren's syndrome, diabetes mellitus) or other specific causes (e.g. refractory surgery, chemical injuries); (2) trials with other interventions except AC or aT (e.g. herbal medicine, moxibustion, electric stimulation); and (3) trials showing unclear data or incomplete information for meta-analysis.

Data extraction

Relevant information and outcome data were extracted by two reviewers (S.C.H. and P.J.G.) independently. Relevant information included first author, year of publication, study design of interventions, sample size, participant characteristics (i.e. mean age, male/female ratio) and treatment protocol (i.e. treatment sessions, duration and frequency, needle-inserting time, number of acupoints). The details were summarized using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark, 2014). Outcome data were obtained from clinical tests of BUT, Schirmer test and CFS, and self-assessment measures of OSDI, VAS and SOS. The data were expressed as the mean and standard deviation of values in post- to pretreatment, with sample sizes of eyes measured, and they were used for meta-analysis. Follow-up data were not included due to a few reports.

Assessment of risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool based on six items (Fig. 2) (Higgins et al. 2011). Each item was judged to have low-, unclear- or high risk of bias by two reviewers (S.C.H. and P.J.G.). Herein, double-blinding was methodologically impossible in the RCTs because of study characteristics requiring a single clinician for acupuncture and no use of a corresponding sham acupuncture. Thus, blinding was assessed separately in the clinical tests and self-assessment measures: clinical tests via the established method were assessed as low risk, while self-assessment measures were considered high risk (Higgins & Green 2011). Other biases were determined according to descriptions of baseline data of participants. Disagreements were resolved through discussion with the other reviewers (N.J.H. and J.J.H.). Inadequate information precluding reliable judgement of risks was deemed as 'high risk' or 'unclear risk' by considering whether the bias may affect the outputs.

Statistical analysis

Statistical analyses were conducted using R version 3.4.1 (The R Foundation, Vienna, Austria). Heterogeneity across studies was determined graphically using forest plots (Lewis & Clarke 2001) and statistically using Higgins I^2 tests (Higgins et al. 2003). As all studies had significant heterogeneity ($p < 0.10$, $I^2 > 50\%$), a random effects model was used for meta-analysis. Results were expressed as average mean differences (MDs) with 95% confidence intervals (CIs). The MD was weighted by inverse variances. It was considered significantly different when 95% CIs did not cross the cut-off point of zero. A sensitivity analysis was performed by leaving each RCT out sequentially and comparing the model characteristics (Higgins & Green 2011). Publication bias was assessed by visual inspection of funnel plots including Egger's test (Egger et al. 1997), and the asymmetry was adjusted by trim and fill method (Duval & Tweedie 2000). For subgroup analyses, meta-regressions analysis was used to explore whether covariates accounted for the heterogeneity. The results were represented as regression coefficients with proportion of variance

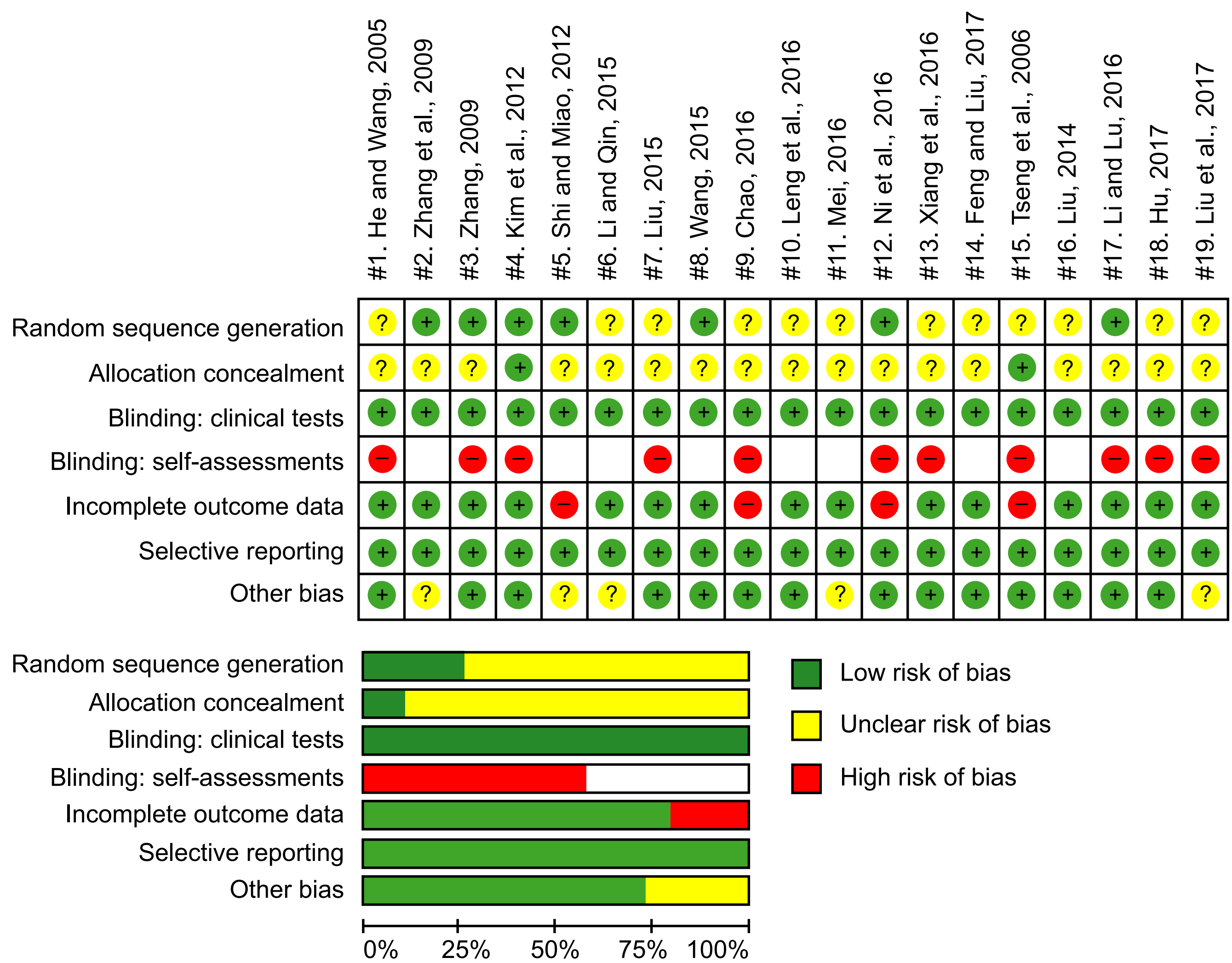


Fig. 2. Risk of bias assessment. '+': low risk, '–': high risk, and '?': unclear. [Colour figure can be viewed at wileyonlinelibrary.com]

in the outcome (R^2). Significance was considered as less than 0.05. Further, Bayesian network meta-analysis was performed to synthesize direct and indirect evidence for an acupuncture sessions in DES (Gurusamy et al. 2016). The Markov chain Monte Carlo method using *rjags* and *gemtc* packages was used, and three chains were fit in each with 50 000 burn-ins and 100 000 iterations. The pooled relative effect sizes were expressed as posterior medians and 95% credible intervals.

Results

Characteristics of studies retrieved

A total of 551 studies were identified, and 19 were finally selected (Fig. 1). The eligible studies are listed in Table 1: fourteen (#1 – #14) and five (#15 – #19) studies were compared between groups of AC and aT (AC vs. aT) and between groups of AC + aT and aT (AC + aT vs. aT), respectively. Four studies (#4, #5, #15 and #19) were written in English and the others in Chinese. Two studies (#1 and #12) performed two independent trials at different acupoints, and the RCTs were identified separately as 'a' and 'b'. Totally, 21 RCTs included 1214 participants (1542 eyes). The mean age ranged from 33.0 to 60.8 years, and females outnumbered males at 60.0% of the total. Acupuncture was treated at 27 acupoints on 10 meridians or 4 extra points in the head and neck: the acupoints were mostly on the head and neck (18 acupoints), and the others were on the upper- (4 acupoints) or lower-limbs (9 acupoints; Fig. S1). The acupuncture was performed at a frequency of 2.0–3.0 (in 11 RCTs) or 3.7–7.0 times per week (in 10 RCTs). Herein, a frequency more and less than half the week (3.5-times/week) was regarded as high and low frequency, respectively. Treatment duration was divided into short term, 21–30 days (in 15 RCTs) and long term, 51, 56 or 90 days (in 6 RCTs).

Study quality based on risk of bias

All studies mentioned regarding the randomization of participant, however, risk of the selection bias was hard to determine due to the lack of information (Fig. 2). The randomization sequence process and allocation concealment were described only in seven (#2, #3, #4, #5, #8, #12 and #17) and two (#4 and #15) studies, respectively, which was assessed as low risk. Blinding to the clinical tests was assessed to introduce low risk of bias in the studies mentioning the established methods, while the self-assessments were considered high risk in 11 studies reporting OSDI, VAS or SOS. Nevertheless, all studies were regarded as having the bias to some degree because sham control acupuncture was not used.

Table 1. Characteristic of studies of acupuncture for treating dry eye syndrome

Studies	Artificial tear (aT)	Acupuncture (AC)	Freq./ Days	Treated acupoints
1. He & Wang (2004)†	(n = 20): 5 times	a: (*n* = 20) 25 min, 30 times b: (*n* = 20) 25 min, 30 times	2.3/90	GB34, KI3, LI4, LI11, LI20, SP6, SP10, ST2, ST36, ST40 BL2, GB14, ST1, TE23
2. Zhang et al. (2009)	(*n* = 30): 3–6 times	(*n* = 30) 20 min, 70 times	5.4/90	KI3, LR3, ST1
3. Zhang (2009)	(*n* = 26): 6 times	(*n* = 28) 30 min, 24 times	6.0/28	BL1, BL2, EX-HN5, GB1, TE23
4. Kim et al. (2012)	(*n* = 75): >1 time	(*n* = 75) 20 min, 12 times	3.0/28	BL2, EX-HN5, GB14, GB20, GV23, LI4, LI11, ST1, TE23
5. Shi & Miao (2012)	(*n* = 34): 3–4 times	(*n* = 31) 25 min, 9 times	3.0/21	BL1, EX-HN5, GV20, LI4, ST1, ST36, TE23
6. Li & Qin (2015)†	(*n* = 12): 3 drops	(*n* = 12) 30 min, 24 times	6.0/28	BL1, BL2, EX-HN5, GB1, TE23
7. Liu (2015)	(*n* = 50): 3 times	(*n* = 50) 30 min, 28 times	7.0/28	BL2, EX-HN4, EX-HN5, GB20, GV20, LI4, SP6, ST1, TE23
8. Wang (2015)	(*n* = 28): 4 times	(*n* = 28) 30 min, 48 times	6.6/51	BL1, BL2, EX-HN5, EX-HN7, GB20, GV20, LI4, SP6, ST2, ST36
9. Chao (2016)†	(*n* = 16): 4 times	(*n* = 19) 30 min, 28 times	7.0/28	BL2, EX-HN5, GB20, GB37, KI3, LR3, SP6, ST2, ST36
10. Leng et al. (2016)	(*n* = 29): 3–6 drops	(*n* = 29) 30 min, 9 times	3.0/21	BL1, BL2, EX-HN5, GB1, TE23
11. Mei (2016)†	(*n* = 34): 4 drops	(*n* = 30) 30 min, 13 times	3.0/30	BL1, BL2, EX-HN4, EX-HN5, KI3, LI4, LU10, ST1, TE23
12. Ni et al. (2016)	(*n* = 31): 5 times	a: (*n* = 30): 20 min, 9 times b: (*n* = 32): 20 min, 9 times	3.0/21	BL1, EX-HN7, GV26, KI3, SP6 BL1, EX-HN7, KI3, SP6
13. Xiang et al. (2016)	(*n* = 44): 4 drops	(*n* = 44): 30 min, 11 times	3.7/21	BL1, BL2, ST2, TE23
14. Feng & Liu (2017)	(*n* = 33): 3–6 times	(*n* = 33): 30 min, 13 times	3.0/30	BL1, EX-HN3, EX-HN5, GB20, GV20, LI4, SP6
15. Tseng et al. (2006)†	(*n* = 17): NR	(*n* = 9): 20 min, 16 times	2.0/56	EX-HN5, GB14, SP6, ST2, TE23
16. Liu (2014)	(*n* = 45): 4–5 drops	(*n* = 45): 30 min, 28 times	7.0/28	BL1, BL2, EX-HN5, GB20, GV20, ST2, TE23
17. Li & Lu (2016)†	(*n* = 16): 3–4 times	(*n* = 17): 30 min, 30 times	7.0/30	BL2, GB14, GB37, KI3, LI4, LR3, SP10, ST2, ST36, TE17, TE23
18. Hu (2017)	(*n* = 30): 4 drops	(*n* = 34): 30 min, 28 times	7.0/28	BL2, EX-HN5, GB14, GV20, GV26, LR3, LU9, SP3, ST2
19. Liu et al. (2017)†	(*n* = 14): NR	(*n* = 14): 30 min, 24 times	3.0/56	BL2, BL3, EX-HN5, GB20, GV20, LI4, ST1, ST2, TE23

Treatment is indicated as drop times or numbers (one eye-drop contains about a volume of 0.05 ml) per day in aT and as a needle-inserting time with the total numbers in the AC. The acupuncture frequency (Freq., times/week) and treated days are indicated. Sample size (*n*) is expressed as a number of participants. The results were assessed in one eye or both eyes (†). Acupoints are on meridians of bladder (BL), gallbladder (GB), governor vessel (GV), kidney (KI), large intestine (LI), liver (LR), lung (LU), spleen (SP), stomach (ST) and triple energizer (TE) and on extra points in head & neck (EX-HN). NR = not reported.

For attrition bias, four studies were assessed as high risk: three (#5, #9 and #12) excluded the data of drop outs in the analyses, and one (#15) had missing data on two patients in Schirmer test. The others were assessed as low risk. Selective bias was assessed as low risk in all, because all outcomes described in their respective methods were reported. While other bias was assessed as unclear-risk in five studies (#2, #5, #6, #11 and #19) with no information, it was assessed as low risk in the others comparing characteristics of data at baseline.

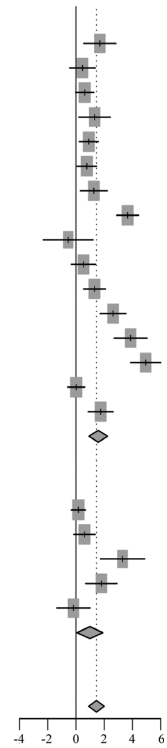
Meta-analysis comparing acupuncture with artificial tears

BUT: All 21 RCTs (n = 1540) compared BUT between the experimental groups (AC and AC + aT) and the control (aT) after the intervention (Fig. 3A). There was a significant increase in the experimental group versus the control (p < 0.01). In subgroup analyses, the random effects models also showed significant increases in the AC vs. aT and the AC + aT vs. aT (p < 0.01).

Schirmer test: 21 RCTs (n = 1542) compared the results (Fig. 3B). The random effects model showed a significant increase in the experimental group versus the control (p < 0.01). In subgroup analyses, there were also significant increases in the AC vs. aT and in the AC + aT vs. aT (p < 0.01).

CFS: 10 RCTs (n = 711) analysed CFS (Tables 2 and S1). Although the methods were different among RCTs, such as fluorescein dye used, divided corneal area, and the scoring manner, the model showed significant decreases in the AC vs. aT (p < 0.05).

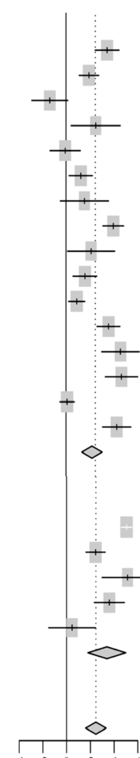
OSDI, VAS and SOS: 3 RCTs analysed OSDI (n = 281) and VAS (n = 276) (Tables 2 and S1). The OSDI and VAS were pooled using a random effects model. Both outputs had no significances in the experimental group versus the control. For SOS, eight RCTs (n = 562) compared the results. The random effects model showed significant decreases in the AC vs. aT (p < 0.01).



Tear-film breakup time (BUT)

Studies	Mean ± standard deviation (n) Experimental	Control	MD [95% CI]	Weight
AC vs. aT				
#1a. He & Wang (2005)	6.70 ± 3.01 (40)	5.01 ± 2.19 (40)	1.69 [0.54; 2.84]	4.5%
#1b. He & Wang (2005)	5.47 ± 2.00 (40)	5.01 ± 2.19 (40)	0.46 [-1.46; 1.38]	4.8%
#2. Zhang et al. (2009)	5.37 ± 1.25 (30)	4.75 ± 1.34 (30)	0.62 [-0.04; 1.28]	5.2%
#3. Zhang (2009)	5.21 ± 2.69 (28)	3.89 ± 1.35 (26)	1.32 [0.20; 2.44]	4.6%
#4. Kim et al. (2012)	6.80 ± 2.25 (75)	5.89 ± 2.02 (75)	0.91 [0.23; 1.59]	5.1%
#5. Shi & Miao (2012)	4.45 ± 1.46 (31)	3.68 ± 1.41 (34)	0.77 [0.07; 1.47]	5.1%
#6. Li & Qin (2015)	5.22 ± 2.02 (24)	3.95 ± 1.31 (24)	1.27 [0.37; 2.23]	4.8%
#7. Liu (2015)	7.35 ± 2.44 (50)	3.69 ± 1.41 (50)	3.66 [2.88; 4.44]	5.0%
#8. Wang (2015)	5.62 ± 3.32 (28)	6.17 ± 3.45 (28)	-0.55 [-0.32; 1.22]	3.6%
#9. Chao (2016)	4.95 ± 2.14 (38)	4.42 ± 1.56 (32)	0.53 [-0.34; 1.40]	4.9%
#10. Leng et al. (2016)	5.23 ± 1.80 (29)	3.92 ± 1.20 (29)	1.31 [0.52; 2.10]	5.0%
#11. Mei (2016)	5.70 ± 2.63 (60)	3.07 ± 2.71 (68)	2.63 [1.70; 3.56]	4.8%
#12a. Ni et al. (2016)	8.87 ± 2.91 (30)	5.00 ± 1.55 (31)	3.87 [2.69; 5.05]	4.5%
#12b. Ni et al. (2016)	9.94 ± 2.68 (32)	5.00 ± 1.55 (31)	4.94 [3.86; 6.02]	4.6%
#13. Xiang et al. (2016)	4.91 ± 1.44 (44)	4.89 ± 1.51 (44)	0.02 [-0.60; 0.64]	5.2%
#14. Feng & Liu (2017)	11.76 ± 1.67 (33)	10.01 ± 2.01 (33)	1.75 [0.86; 2.64]	4.9%
Random effects model	(612)	(615)	1.58 [0.91; 2.25]	76.8%
Heterogeneity: I^2 = 89%, p < 0.01				
AC+aT vs. aT				
#15. Tseng et al. (2006)	6.45 ± 0.68 (27)	6.28 ± 0.91 (16)	0.17 [-0.34; 0.68]	5.3%
#16. Liu (2014)	5.46 ± 1.98 (45)	4.86 ± 1.74 (45)	0.60 [-0.17; 1.37]	5.0%
#17. Li & Lu (2016)	15.14 ± 3.21 (30)	11.84 ± 3.04 (30)	3.30 [1.72; 4.88]	3.9%
#18. Hu (2017)	8.16 ± 2.47 (34)	6.36 ± 2.12 (30)	1.80 [0.68; 2.93]	4.6%
#19. Liu et al. (2017)	4.57 ± 2.71 (28)	4.75 ± 1.74 (28)	-0.18 [-1.37; 1.01]	4.5%
Random effects model	(164)	(149)	0.99 [0.05; 1.92]	23.2%
Heterogeneity: I^2 = 80%, p < 0.01				
AC and AC+aT vs. aT				
Random effects model	(776)	(764)	1.45 [0.89; 2.01]	100.0%
Heterogeneity: I^2 = 89%, p < 0.01				

(A)



Schirmer test

Studies	Mean ± standard deviation (n) Experimental	Control	MD [95% CI]	Weight
AC vs. aT				
#1a. He & Wang (2005)	6.43 ± 2.95 (40)	2.97 ± 1.43 (40)	3.46 [2.44; 4.48]	5.0%
#1b. He & Wang (2005)	4.90 ± 2.30 (40)	2.97 ± 1.43 (40)	1.93 [1.09; 2.77]	5.1%
#2. Zhang et al. (2009)	7.44 ± 2.22 (30)	8.81 ± 3.66 (30)	-1.37 [-2.90; 0.16]	4.6%
#3. Zhang (2009)	6.79 ± 4.67 (28)	4.29 ± 3.01 (26)	2.50 [0.42; 4.58]	4.1%
#4. Kim et al. (2012)	4.88 ± 3.70 (75)	4.95 ± 4.34 (75)	-0.07 [-1.36; 1.22]	4.8%
#5. Shi & Miao (2012)	6.00 ± 2.02 (31)	4.76 ± 2.05 (34)	1.24 [0.25; 2.23]	5.0%
#6. Li & Qin (2015)	5.18 ± 4.15 (24)	3.63 ± 2.98 (24)	1.55 [-0.49; 3.59]	4.1%
#7. Liu (2015)	7.17 ± 2.73 (50)	3.19 ± 1.70 (50)	3.98 [3.09; 4.87]	5.1%
#8. Wang (2015)	7.73 ± 4.26 (28)	5.62 ± 3.32 (28)	2.11 [0.11; 4.11]	4.2%
#9. Chao (2016)	6.00 ± 2.36 (38)	4.41 ± 1.97 (32)	1.59 [0.58; 2.60]	5.0%
#10. Leng et al. (2016)	5.10 ± 1.40 (29)	4.20 ± 1.30 (29)	0.90 [0.21; 1.60]	5.2%
#11. Mei (2016)	7.11 ± 3.03 (60)	3.53 ± 2.59 (68)	3.58 [2.60; 4.56]	5.0%
#12a. Ni et al. (2016)	10.17 ± 3.61 (30)	5.58 ± 2.67 (31)	4.59 [3.00; 6.19]	4.5%
#12b. Ni et al. (2016)	10.25 ± 2.92 (32)	5.58 ± 2.67 (31)	4.67 [3.29; 6.05]	4.7%
#13. Xiang et al. (2016)	6.59 ± 1.45 (44)	6.50 ± 1.50 (44)	0.09 [-0.53; 0.71]	5.2%
#14. Feng & Liu (2017)	13.69 ± 2.47 (33)	9.42 ± 2.54 (33)	4.27 [3.06; 5.48]	4.9%
Random effects model	(612)	(615)	2.18 [1.32; 3.05]	76.6%
Heterogeneity: I^2 = 90%, p < 0.01				
AC+aT vs. aT				
#15. Tseng et al. (2006)	7.54 ± 0.58 (29)	2.48 ± 0.80 (16)	5.06 [4.62; 5.51]	5.3%
#16. Liu (2014)	5.41 ± 2.41 (45)	2.97 ± 1.42 (45)	2.44 [1.62; 3.26]	5.1%
#17. Li & Lu (2016)	18.41 ± 4.31 (30)	13.27 ± 4.24 (30)	5.14 [2.98; 7.30]	4.0%
#18. Hu (2017)	8.96 ± 2.78 (34)	5.36 ± 2.46 (30)	3.60 [2.32; 4.88]	4.8%
#19. Liu et al. (2017)	5.89 ± 4.51 (28)	5.43 ± 2.91 (28)	0.46 [-4.53; 2.45]	4.2%
Random effects model	(166)	(149)	3.39 [1.78; 5.00]	23.4%
Heterogeneity: I^2 = 92%, p < 0.01				
AC and AC+aT vs. aT				
Random effects model	(778)	(764)	2.46 [1.59; 3.34]	100.0%
Heterogeneity: I^2 = 94%, p < 0.01				

(B)

Fig. 3. Forest plots of meta-analysis. Experimental group was treated with acupuncture (AC) or its combination with artificial tears (AC + aT), and it was compared with the control (aT). The value is represented as mean ± standard deviation after treatments. Output of meta-analyses for BUT (A) and Schirmer test (B) is represented as mean differences (MDs) and 95% confidence intervals (CIs). The MD was weighted by inverse variances.

Table 2. Meta-analyses for corneal fluorescence staining and self-assessments

		Heterogeneity		Random effects model	
Indexes	RCTs (*n*)	I^2 (%)	*p*-value	MD [95% CI]	*p*-value
Corneal fluorescence staining	10	54	0.02	−0.25 [−0.45, −0.05]	0.01
Ocular surface disease index	3	98	< 0.01	−4.25 [−9.72, 1.22]	0.13
Visual analogue scale	3	98	< 0.01	−0.16 [−2.49, 2.17]	0.89
Symptom of score	8	68	< 0.01	−2.55 [−3.57, −1.53]	<0.01

Experimental group was treated with acupuncture (AC) or its combination with artificial tears (AC + aT), and it was compared with the control (aT). Output of meta-analyses is represented as mean differences (MDs) and 95% confidence intervals (CIs).

Sensitivity analysis and publication bias

Sensitivity analysis: When omitting each RCT, there were no changes in the significant outputs from meta-analyses for BUT, Schirmer test and SOS (Fig. S2). However, there was a significant impact in the outputs of CFS ($p = 0.01$): omitting RCT #11 showed no significance in the results ($p = 0.07$).

Publication bias: The funnel plot and the Egger's test showed significant asymmetry in the outputs of BUT (Coefficient: −0.77, $p < 0.05$), indicating high heterogeneity (Fig. S3). However, the significance in meta-analyses was not changed by trim and fill method (MD = 0.86, CI: 0.17–1.56, $p < 0.05$). There was no significant asymmetry in the Schirmer test and CFS. However, application of trim and fill method to the CFS showed changes to be non-significant in the outputs (MD = −0.22, CI: −0.44 to 0.00, $p = 0.05$). Thus, correlations between various covariates and outputs of the meta-analyses were examined focused on the BUT and Schirmer test as being more informative.

Correlation between covariates and outputs of meta-analysis

Meta-regression analysis: There was no significance between study quality and the outputs of BUT or Schirmer test (Table 3). Among variables (participant number, age and sex), only age showed a negative correlation with the outputs of BUT ($p < 0.05$), indicating the younger the better effects. There were no correlations between treatment protocols (treatment sessions, duration and frequency and the number of acupoints used) and the outcomes of BUT or Schirmer test. Although it failed to reach to significance, the correlation between the acupuncture duration and the outputs of BUT showed borderline significance ($p = 0.06$). Thus, the analysis was examined in the RCTs divided according to acupuncture periods and frequency. The improved BUT was significantly correlated with short-term acupuncture at all frequencies, especially the short term at a low frequency ($p < 0.05$), compared to the long-term treatment.

Network meta-analysis: There were significances in the improved BUT and Schirmer test in short-term acupuncture regardless of frequency, as compared to the aT group (Table 4). Long-term acupuncture at a low frequency versus the aT also showed possibilities to improve Schirmer test.

Table 3. Meta-regression analyses between covariates and outputs of meta-analyses

	Tear-film breakup time (BUT)			Schirmer test		
Covariates	coefficient	R^2 (%)	p-value	coefficient	R^2 (%)	p-value
In all RCTs						
Study quality	−2.23	0.00	0.31	−0.16	0.00	0.96
Participant number	0.01	0.00	0.54	−0.02	19.05	0.26
Participant age	−0.10	4.32	0.03	−0.05	0.00	0.50
Participant sex	−1.35	0.00	0.57	−2.12	0.00	0.56
Treated duration	−0.03	2.43	0.06	−0.03	6.38	0.21
Treated times (aT)	0.02	0.00	0.96	0.36	0.00	0.48
Treated times (AC)	−0.03	0.00	0.20	−0.04	0.00	0.23
Treated frequency (AC)	0.04	0.00	0.81	−0.01	0.00	0.96
Number of acupoints (AC)	0.02	0.00	0.86	0.16	0.00	0.40
In RCTs divided by AC for short vs. long term						
At all frequencies	–	11.57	0.02	–	8.44	0.56
At a high frequency	−1.38	0.00	0.22	−2.27	4.27	0.13
At a low frequency	−1.72	21.47	0.03	0.16	10.86	0.89
In RCTs divided by AC at high vs. low frequency						
For all duration	–	0.00	0.59	–	6.54	0.47
For a short term	0.74	0.00	0.31	−0.15	0.00	0.88
For a long term	−0.14	0.00	0.82	−2.56	31.54	0.16

Correlations between covariates and outputs of meta-analyses for BUT and Schirmer test were analysed in all randomized controlled trials (RCTs) comparing experimental group including acupuncture treatment (AC) with artificial tears (aT). It was further examined in RCTs divided by acupuncture protocol.

Discussion

We retrieved 21 RCTs of acupuncture in non-specific DES from all articles published to June 2018. Only one more RCT has been until July 2020 through the databases of PubMed, Medline, Web of Science and Cochrane (Tong et al. 2018), but it was not included in this study. The present meta-analyses revealed the superiority of acupuncture in improving BUT, Schirmer test, CFS and SOS in typical DES, but also greater effects of the combination with artificial tears on the BUT and Schirmer test, compared with artificial tears alone. The outputs of OSDI and VAS were not significant probably due to the small sample sizes of three RCTs, although they tended to be alleviated by acupuncture. The sensitivity analysis and the publication bias for more rigorous quality control of the meta-analysis supported the stability of the results. The subgroup analyses suggest that acupuncture protocol for 21–30 days at a 2–3 times per week can be optimal for treating typical DES. However, the effects of acupuncture in RCTs for the meta-analyses were not compared with those of the sham acupuncture control. Skin stimulation even via non-penetrating sham acupuncture can activate the sensory-discriminative pathways including pain sensation and induce the psychological expectation and physiological changes, affecting especially in the patient-

Table 4. Network meta-analysis on acupuncture duration and frequency

aT	0.49 [−1.81, 2.72]	0.52 [−0.98, 2.08]	**1.47 [0.40, 2.57]**	**2.25 [1.13, 3.40]**
2.31 [−0.96, 5.47]	**Long term at high frequency**	0.04 [−2.67, 2.78]	1.00 [−1.48, 3.55]	1.77 [−0.71, 4.35]
2.86 [0.71, 4.97]	0.58 [−3.32, 4.42]	**Long term at low frequency**	0.95 [−0.92, 2.82]	1.73 [−0.18, 3.63]
2.08 [0.58, 3.62]	−0.21 [−3.79, 3.41]	−0.78 [−3.31, 1.88]	**Short term at high frequency**	0.77 [−0.78, 2.35]
2.71 [1.11, 4.30]	0.39 [−3.19, 4.03]	−0.18 [−2.78, 2.54]	0.63 [−1.61, 2.83]	**Short term at low frequency**

Effects of acupuncture duration and frequency on the outputs were examined by network meta-analysis. Grey cells indicate control group treated with artificial tear (aT) and experimental groups with acupuncture for up to 30 days (short term) or more than 50 days (long term) at more and less than 3.5-times per week (high and low frequency, respectively). Tear-film breakup time (BUT) and Schirmer test (upper and lower cells of the grey, respectively) were compared between the groups in a direction of left to right cells for the BUT and upper to lower for the Schirmer test. Values are expressed as posterior medians [95% confidence intervals]. Bold values mean significances.

reported outcomes. Thus, we focused on the meta-analyses for the objective results of BUT and Schirmer test, and however, the placebo effect could not be still ruled out.

There have been five meta-analysis studies on the efficacy of acupuncture in DES (Lee et al. 2011; Ba et al. 2013; Yang et al. 2015; Jiang et al., 2017a; Kim et al. 2018). In agreement with our results, these studies showed significant increases in the outputs of BUT and Schirmer test in treatments of acupuncture versus artificial tears. In addition, they reported the beneficial effects on CFS (Lee et al. 2011; Ba et al. 2013; Yang et al. 2015; Kim et al. 2018) or self-assessments of response ratios for effectiveness (Lee et al. 2011; Ba et al. 2013). Only one meta-analysis reported significant increases in Schirmer test in acupuncture in combination with artificial tears versus artificial tears alone (Kim et al. 2018). However, some RCTs used for the meta-analyses were unsuitable for our eligibility as following reasons: they are non-RCTs (Gao et al. 2010), or they include participants with Sjögren's syndrome (Pang et al. 2003; He et al. 2004), acupuncture at non-acupoints (Nan 2014; Zhang et al., 2015) or acupuncture with other interventions (Zhang & Yang 2007; Liu et al. 2009; Wei et al. 2010). Based on our eligibility criteria, the previous meta-analyses for BUT and Schirmer test could include up to eight RCTs: two of the original three RCTs in Lee et al. (2011), five of the six in Yang et al. (2015), four of the six in Jiang et al. (2017a), six of the nine in Ba et al. (2013) and eight of the twelve in Kim et al. (2018). This means that our results from the meta-analyses including 21 RCTs can be considered more reliable for the effectiveness of acupuncture and its combination with artificial tears in typical DES.

There were high heterogeneities across the RCTs in the meta-analysis, so meta-regression analyses were conducted to determine the source of the heterogeneity. Although the study quality and participant sex had no correlation with the outputs, ageing showed negative correlations with the improvement in BUT, but not in Schirmer test. Increasing age is one of major risk factors for DES, and results of BUT and Schirmer test generally reduce with ageing (Bhavsar et al. 2011). Although age-dependent placebo effects could not be ruled out, acupuncture might improve the tear-film quality within a range of age-dependent physiological functions in patients with DES, but increase the tear-film quantity regardless age. Besides, the subgroup analysis revealed that the acupuncture protocol depending on treatment duration and frequency as the integral parts could be a major source of the high heterogeneity. Indeed, the acupuncture protocol was varied among the 21 RCTs in this study, and it was different even between traditional Chinese and Korean acupuncture for treating DES. This means an urgent need to establish optimal guidelines for the treatment of DES. One previous meta-analysis reported the optimized protocol for DES: acupuncture can be more effective in the treatment more than 30 days than shorter treatment, and more at a frequency more than three times than less frequency (Kim et al. 2018). Conversely, the current study showed that results of BUT and Schirmer test can be improved more by acupuncture for up to 30 days than by longer treatment, especially at low frequencies. This suggests that the therapeutic potential of acupuncture for typical DES can be maximized in the harmonized combination of specific acupoints with the protocol of a short term and low frequency.

Acupuncture is regarded as one of treatment options for DES, but the therapeutic mechanisms remain to be clarified. The relevant mechanism is expected to involve promoting secretion of tears (Liu et al. 2017), reducing pain and inflammation (Nepp et al. 2002), increasing the ocular blood flow (Newberg et al. 2005) and regulating the nervous and immune system (Kavoussi & Ross 2007; Zhang et al. 2012). There are a few animal studies to support the evidences; acupuncture increases the lacrimal secretion by stimulating the lacrimal glandular function of synthesis and secretion in DES rabbit model, but also increases the tear protein quantity in normal rabbit (Gong & Sun 2007; Qiu et al. 2011). In addition, foot acupuncture increases the ocular blood flow in mice (Nishinaka et al. 2020) and acupunctures including ST36 inhibit the systemic and local inflammation via neural and immune pathways (Kim et al. 2007; Song et al. 2014). However, the mechanism based on specific acupoints for treating typical DES is more difficult to analyse because of a lack of studies. Meridian including several hundred acupoints is traditionally regarded as the primary target of acupuncture to correct the imbalance of energy flow referred to as *Qi*. In the traditional acupuncture, DES is classified as the liver *yin* deficiency, which can be nourished mainly by the kidney (KI) meridian, particularly KI3 (Sun 2007). To now, acupuncture at BL1 close to the lacrimal gland stimulates tear secretion in DES (Zhang et al. 2018), and KI3 and LI4 involve improvements in visual function by activating the visual-associated cortex in cognitive impairments (Chen et al. 2014) and in circulation of the facial blood and function of the facial nerves in Bell's palsy, respectively (Guan et al.

2012). It has also been reported that GV20 and ST36 inhibit secretion of inflammatory cytokines in depression (Sun et al. 2010), and SP6 has analgesic effects in dysmenorrhoea (Zhi 2007). However, it is enigmatic how the specific acupoints modulates the nervous and immune system in typical DES.

There are several limitations in this study. First, the retrieved RCTs have no valid placebo groups or appropriate treatment masking, with similar difficulties in other procedural therapies (i.e. surgery). However, sham acupuncture control may not induce the floor effects because of psychological and physiological changes (Lund & Lundeberg 2006), and most of patients distinguish the non-penetrating sham acupuncture control from the true acupuncture. Besides, the double-blind trials of acupuncture are hard to conduct because the trials require one expert practitioner, and the cross-over trials may be more inappropriate due to possible long-term effects. To the best of our knowledge, there have been three RCTs comparing true acupuncture with a sham control (Shin et al. 2010; Jiang et al., 2017b; Dhaliwal et al. 2019). Although two RCTs included patients with Sjögren's syndrome or evaporative dry eye (Jiang et al., 2017b; Dhaliwal et al. 2019), all of the RCTs report lack of efficacy soon after acupuncture with placebo effects but significant improvement in long-term follow-up. Similarly, one RCT (#4) showed no significance just after the treatments of acupuncture versus artificial tears, but improvements were observed in the acupuncture group at the 8-week follow-up (Kim et al. 2012). These might be associated with the cumulative effect of acupuncture. Further studies need to clarify the long-term effects of acupuncture in DES.

This study demonstrates for the first time that acupuncture and its combination with artificial tears may be more effective in non-specific typical DES than the artificial tears alone. Further, the subgroup analyses suggested the optimal acupuncture session. It is widely held opinion that acupuncture is safe in the hands of well-trained practitioners (Zhang et al. 2010). Therefore, our results are valuable for guiding more detailed studies in patients with DES.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Body regions of acupoints used in RCTs.
Figure S2. Sensitivity analysis on outputs of meta-analyses.
Figure S3. Funnel plots for reporting bias.
Table S1. Outputs of meta-analyses for corneal fluorescence staining and self-assessment measures.