

안구건조증에 대한 한의 임상연구 동향에 관한 조사

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Research Trend of Clinical Trials on Dry Eye Syndrome using Korean Medicine Treatment

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Abstract

This study aims to review the trend of clinical research on dry eye syndrome using Korean medicine. Studies published after 2010 were selected through three international online databases (PubMed, Cochrane Library, CNKI) and two domestic online databases (Science on, OASIS). Only clinical researches were selected and analyzed with the research method. A total of 19 studies related to dry eye treatment were conducted for the past ten years. Acupuncture and herbal medicine were the most frequently used treatment methods. Evaluation tools to measure the patients' improvement were SIT (Schirmer I test), OSDI (Ocular Surface Disease Index), and BUT (Tear film break-up time). Korean medicine had superior therapeutic effects for dry eye syndrome treatment compared to artificial tear treatment, and the most frequently used treatment method was acupuncture treatment.

Keywords: dry eye, research trend, acupuncture, herbal medicine, traditional Korean medicine

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Introduction

Dry eye syndrome, which is also called “Guansungan (乾性眼)”¹⁾, is an umbrella term for ocular surface damage that results from instability of the tear film and decreased or abnormal tear production²⁾. Symptoms include discomfort, itchy feeling in the eyes, redness of the eyes, dry and feeling tiredness in the eyes³⁾. Treatment of dry eye includes artificial tear, punctual occlusion, therapeutic contact lens, blepharorrhaphy, and etc⁴⁾. However, as the majority of people use mobile devices and spend more time indoors the complaint rate of eye strain and dryness has increased than in the past, and these factors may exacerbate dry eye syndrome. According to the National Health Insurance Service, the number of patients with dry eye is steadily increased; in 2010, the number of patients with dry eye were 1,860,000; in 2015, it increased to 2,150,000; in 2019 it increased to 2,380,000. In Korean medicine, dry eye is called “白澁”, “乾澀昏花”, “腫人乾缺” and etc. “風”, “津液虧損” and “火”⁵⁾ are known to cause dry eye, and treatments for dry eyes include intradermal acupuncture⁶⁾, pharmacopuncture⁷⁾, moxibustion⁸⁾, and etc. Numerous clinical studies on Korean medicine treatment of dry eye syndrome have been conducted but the research trend of clinical trials to measure the current situation of Korean medicine treatment is insufficient, especially on acupuncture and herbal medicine. Thus, the purpose of this study is to generally investigate the research trend of clinical trials of dry eye syndrome.

Discussion

1. Methods

1) Data sources

The data was collected by using search engines including foreign online databases, such as PubMed, Cochrane Library, and CNKI (China National Knowledge Infrastructure) and domestic online databases, Science On and OASIS (Korea Institute of Oriental Medicine). Search words for dry eye were ‘dry eye’, ‘xerophthalmia’, ‘dysfunctional tear syndrome’, ‘keratoconjunctivitis sicca’, ‘안구’, ‘건안’, and for treatments were ‘acupuncture’, ‘moxibustion’, ‘herbal medicine’, and ‘Chinese medicine’. The retrieval date was Jan 13, 2021. For PubMed, search words were (“Dry Eye Syndromes”[Mesh] AND (“Acupuncture”[Mesh] OR “Acupuncture Therapy”[Mesh] OR “Acupuncture, Ear”[Mesh] OR “Moxibustion”[Mesh] OR “Medicine, Chinese Traditional”[Mesh]), and for CNKI, the reports were only searched in Title field and other languages.



2) Search strategy

The collected reports were reviewed based on the titles and abstracts. The extracted studies were reviewed once again based on the original document to decide the applicability for the study. Research subjects were clinical researches published after 2010 and before 2021. Systematic reviews, protocol studies and in vitro and in vivo studies were excluded.

3) Searching Result

Based on the database results, 338 articles published domestically and abroad were collected. After removing articles not in full-text, articles in the language of Chinese, Japanese, and German, 90 studies were collected. After this process, 158 unrelated articles were excluded. After removing 71 duplicated articles, a total of 19 studies were selected as the subjects of analysis.

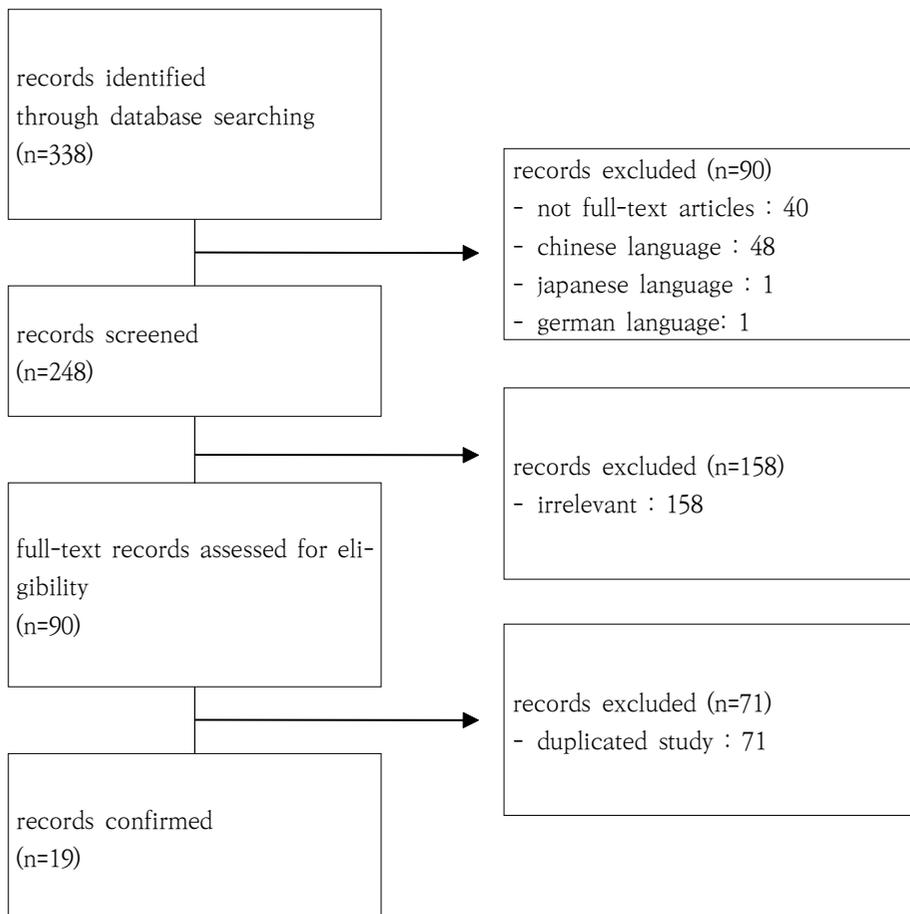


Fig. 1. Flowchart of paper selection process

2. Result

1) Summary of Case report

Among the 19 clinical researches selected, 5 (26.31%) were observational studies and 14 (73.68%) were experimental studies. Chronological analysis of the studies showed 4 published in 2010, 4 published in 2012, 1 published in 2013, 1 published in 2015, 1 published in 2016, 1 published in 2017, 3 published in 2018, 3 published in 2019 and 1 published in 2020. The number of cases are shown in Fig. 2.

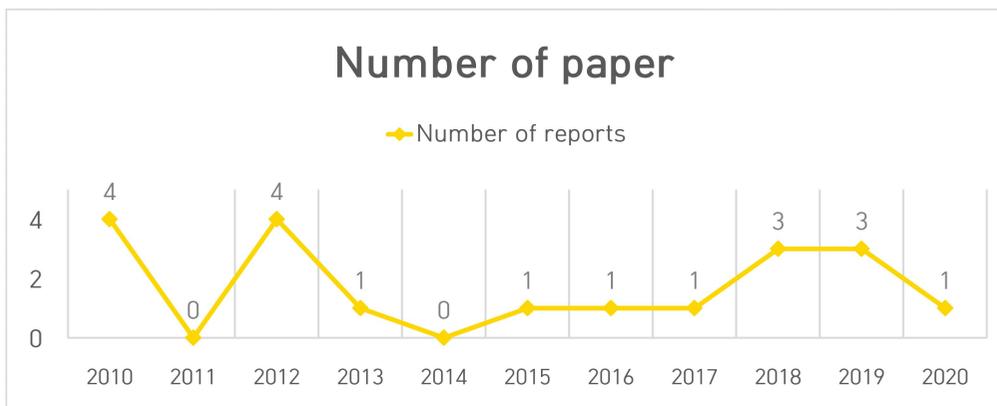


Fig. 2. Number of published studies on dry eye

2) Analysis of treatment

Out of 19 studies, cases using acupuncture only were 14 (73.7%), cases using herbal medicine only were 1 (5.3%), and cases using both acupuncture and herbal medicine were 4 (21%).

(1) Acupuncture

Out of 19 studies, 18 studies used acupuncture treatment. 15 (83.3%) studies used acupuncture, 1 (5.5%) study used pharmacopuncture, 1(5.5%) study used electro-acupuncture and 1 (5.5%) study used thread-embedding therapy for treatment.

Acupoints used for acupuncture treatment were BL2 (12 times), BL1 (8 times), GB20 (9 times), TE23 (6 times), GB14 (6 times), ST1 (6 times) and etc. These acupoints are located in the area around the eyes. In the study by Gong⁹⁾, LI 4, LR 3 and GB 20, etc., can also remove intensive heat from the liver, improve acuity of sight, and remove obstructions in the channels to relieve pain. In the study by Gao¹⁰⁾, BL20 and ST 40 were combined for spleen and stomach damp-heat, BL18 and BL23 were chosen for liver-kidney yin deficiency. The needle was usually retained for 15-30 mins, and

especially 45 mins in Dhaliwal's study¹¹).

For electroacupuncture therapy, patients received low-frequency electrical stimulation and the stimulation was within the patient's tolerance.

For thread-embedding therapy, the needle with the diameter of 0.2 mm, and length of 0.3-1.5 mm, was applied. 0.2 mm × 1.5 mm thread-embedding therapy was adopted at SP6, ST36 and ST40, and 0.2 mm × 0.9 mm thread-embedding therapy was adopted at PC6, LR3, LI4, BL20, BL18 and BL23¹⁰).

For pharmacopuncture treatment, patients were treated with ginseng pharmacopuncture combined with CV13, CV12, CV10, CV15, CV4, ST25 and other pressure points¹²).

(2) Herbal medicine

Out of 19 studies, 5 studies used herbal medicine. Cases using herbal medicine were 3 (60%) and using herbal extracts were 2 (40%). In Chen's study¹²), herbal medicine was used individually based on each patient's diagnosis. For male patients, the main formula was Jesaengsingi-hwan (濟生腎氣丸), and herbs including *Salviae Miltiorrhizae Radix*, *Ligustri Lucidi Fructus*, *Lycii Fructus*, *Chrysanthemi Flos* were combined based on the patient's pattern. For female patients, the main formulas were Ilgwanjeon (一貫煎), Gamisoyo-san (加味逍遙散), Jesaengsingi-hwan (濟生腎氣丸), and herbs including *Saposhnikovia Radix*, *Uncariae Ramulus cum Uncis* were combined.

For female patients on herbal medicine, *Coptidis Rhizoma* 0.4 g and *Amomi Fuctus* 0.6 g were added daily, and Jesaengsingi-hwan (濟生腎氣丸) and Gamisoyo-san (加味逍遙散) were reduced 3g daily.

3) Analysis of measuring tools

SIT (Schirmer I test) was used 14 times to evaluate the outcomes, OSDI (Ocular Surface Disease Index) was used 13 times, BUT (Tear film break-up time) was used 13 times. Also, studies using CFS (Corneal Fluorescein Staining) were 3 cases, while studies using QOL (Quality Of Life) and VAS (Visual Analogue Scale) were 2 for each, and studies that focused on the use of artificial use were 2.

4) Analysis of age and sex

Out of the 19 studies, 13 (68.4%) cases were able to confirm the patient's gender. Based on the results, 261 (32.2%) were male patients and 549 (67.8%) female patients, in the total of 810 patients. In most reports, there were more female patients than males. However, in Liu's study³), there were 60 males and 30 females and in Gao's study¹⁰), there were 55 males and 33 females. In Liu study¹³), 28 postmenopausal women with dry eye disease were in the treatment, in Apriani's study²⁴) was consisted of 69 menopausal women with dry eye and in Zhang's study¹⁴), 60 postmenopausal females diagnosed with dry eye were assigned to treatment.

5) Analysis of adverse event

There were 9 (47.4%) case reports out of 19 that recorded adverse events. Out of the 9 studies, 2 (22.2%) were about hematoma and petechia from acupuncture treatment and 2 (22.2%) were about visual blur and foreign body sensation from artificial tear treatment. Most of these adverse events disappeared in several weeks.

6) Analysis of outcome

In 17 (89.5%) case reports out of 19, acupuncture therapy and herbal medicine had positive effects on the symptoms of dry eye. In Kim's study¹⁵⁾, there was no statistical difference between acupuncture and artificial tear treatment in the assessment of dry eye symptoms after 4 weeks of treatment. However, compared with artificial tear group, the OSDI and VAS were significantly improved in the acupuncture treatment group at 8 weeks after the end of treatment.

3. Discussion

By analyzing 19 case reports collected, acupuncture therapy, herbal medicine and artificial tears were used for dry eye treatment. Current Western treatment of dry eye mainly involves eye-drops which usually provides only temporary symptomatic relief in eye discomfort. Therefore, alternative treatments should be explored¹⁶⁾, and Korean medicine treatment has benefits on outcomes related to dry eye syndrome compared with artificial tears¹⁵⁾.

In acupuncture treatment, not only acupoints around the eye, but also other acupoints based on each patient's diagnosis were used. Effectiveness of acupuncture therapy had a longer continuous effect than that of artificial tears⁹⁾.

In electroacupuncture treatment, electroacupuncture therapy had significant improvements on decreasing OSDI score and increasing SIT²⁵⁾.

In thread-embedding treatment, acupuncture therapy was combined with thread-embedding for the treatment of dry eye. The efficacy of acupuncture combined with thread-embedding was significant and showed improvement in the symptoms of dry eye¹⁰⁾.

For the use of pharmacopuncture, ginseng pharmacopuncture improved not only eye drying, but also foreign body sensation, visual blur and etc. Also, pharmacopuncture based on ginseng radix showed to be effective and safe with no side effects⁷⁾.

For herbal medicine treatment, total 4 case reports used herbal medicine treatment. Compared with the acupuncture treatment group, it was comparatively used fewer times. Out of 4 reports, 2 were herbal extract dry drops and medicinal fumigation. This showed that various herbal-based treatments could be used in dry eye patients.



Treatment outcomes were analyzed by many types of outcome assessments, such as OSDI, SIT, VAS and etc.

The study has analyzed 19 case reports from 2010 to 2020 on dry eye and has reviewed treatment, diagnosis, and outcomes related with dry eye treatment. However, it has limits since the study includes research only written in Korean and English which requires further research.

Conclusion

19 case reports were analyzed in this report to evaluate the research trend of dry eye treatment, evaluating tools and outcomes.

1. From 2010 to 2020, 5 observational studies and 14 experimental studies using Korean medicine treatment were published.
2. Treatments used in studies were acupuncture therapy and herbal medicine, and especially acupuncture treatment was used the most.
3. Evaluating tools to measure the patients' improvement rate were mainly SIT, OSDI, BUT and etc.
4. Improvement of dry eye symptoms in Korean medicine lasted longer than those of artificial tears.

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References

1. Lee SC, Jin KH. Reviews: Dry Eye Syndrome, Journal of kyung hee university medical center. 2006;22(2):107-11.
2. Chu RY, Zhang L. Ophthalmopathy Study. Beijing: People's Medical Publishing House. 2004:50-1.
3. Liu Xin-quan, Zhu Hua-ying, Ruan Wen-jie. Clinical Study on Combined Acupuncture and Chinese Medicinal Fumigation for Dry Eye Syndrome, Journal of Acupuncture Tuina. Science. 2013;11(2):79-83.
4. Kim, Eun Chul. Diagnosis and treatment of dry eye syndrome. Journal of the Korean Medical Association. 2018;61(6):352-64.
5. Jeong DH, Kim JH, Choi JH. A literature of study on Xerophthalmia. The Journal of Korean Medicine Ophthalmology and Otolaryngology Dermatology. 2002;15(1):177-97.



6. Song JH, Park SY. Trend of Clinical Trials for Intradermal Acupuncture Treatment on Dry Eye Syndrome. *The Journal of Korean Medicine Ophthalmology and Otolaryngology Dermatology*. 2020;33(2):12-22.
7. Kang EJ, Park EY, Kim KM. Clinical Effects of Rg3 Ginseng Pharmacopuncture for Dry Eye Syndrome in Six Case Reports. *The Journal of Internal Korean Medicine*. 2018;39(5):929-38.
8. Lee HC, Lee YL, Ko HJ, Choi JW, Jeong MY, Park SY. Systematic Review of Moxibustion Treatment for Dry Eye Syndrome. *The Journal of Korean Medicine Ophthalmology and Otolaryngology Dermatology*. 2019;32(1):42-58.
9. Lan Gong, Xinghuai Sun, William J. Chapin. Clinical Curative Effect of Acupuncture Therapy on Xerophthalmia, *The American Journal of Chinese Medicine*. 2010;38(4):651-9.
10. Gao Hui, Zhao Xiao-dong, Ma Guo-juan, Li Huan-li, Liu Huai-dong. Acupuncture combined with pyonex for xerophthalmia, *World Journal of Acupuncture-Moxibustion*. 2016;26(2):37-42.
11. Deepinder K Dhaliwal, Siwei Zhou, Sandeep S Samudre, Nathan J lo, Michelle K Rhee. Acupuncture and dry eye: current perspectives. A double-blinded randomized controlled trial and review of the literature, *Clinical Ophthalmology*. 2019;13:731-40.
12. Ying-Ling Chen, Mark Chun-Cheng Hou. Acupuncture and Chinese Herbal Treatment for Dry Eye Disease: Two Case Reports, *Medical Acupuncture*. 2012;24(1):50-4.
13. Qingyu Liu, Junling Liu, Chengda Ren, Wenting Cai, Qingquan Wei, Yi Song, Jing Yu. Proteomic analysis of tears following acupuncture treatment for menopausal dry eye disease by two-dimensional nano-liquid chromatography coupled with tandem mass spectrometry, *International Journal of Nanomedicine*. 2017;12:1663-71.
14. Bing Zhang, Pei-Wen Zhu, Qi Lin, Qing Yuan, Biao Li, You-Lan Min, Lei Ye, Wen-Qing Shi, Yi Shao. *Buddleja officinalis* eye drops alleviate the symptoms of moderate to severe dry eye, *International Journal of Clinical and Experimental Medicine*. 2019;12(7):9277-87.
15. Kim TH, Kang JW, Kim KH, Kang KW, Shin MS, Jung SY, Kim AR, Jung HJ, Choi JB, Hong KE, Lee SD, Choi SM. Acupuncture for the Treatment of Dry Eye: A multicenter Randomised Controlled Trial with Active Comparison Intervention (Artificial Teardrops), *PLoS ONE*. 2012;7(5):e36638.
16. Louis Tong, Hla Myint Htoon, Aihua Hou, Rajendra Udyavara Acharya, Jen Hong Tan, Qi-Ping Wei, Pat Lim. Acupuncture and herbal formulation compared with artificial tears alone: evaluation of dry eye symptoms and associated tests in randomized clinical trial, *BMJ Open Ophthalmology*. 2018;3:e000150.
17. Jeon JH, Shin MS, Lee MS, Jeong SY, Kang WK, Kim YI, Choi SM. Acupuncture reduces symptoms of dry eye syndrome: a preliminary observational study, *The journal of alternative and complementary medicine*. 2010;16(12):1291-4.



18. Lee CW, Lee EK, Jeon JH, Kim JH, Kim YI, Kim JI. Effects of acupuncture therapy on dry eye syndrome: 43 case series, The journal of Korean acupuncture & moxibustion society. 2010;27(6):85-93.
19. Kim YS, Park BC, Kim HY, Choi JY, Moon JB, Oh TW, Ma JY, Kim KB. Retrospective Observational Study for Effectiveness of Inmok-tang on Dry Eye Syndrome, Herbal Formula Science. 2019;27(4):285-97.
20. Lee DJ, Hwang-Bo M, Seo HS, Kim SJ, Lee JS. Eastern and western combined medical treatments on 11 patients with dry eye syndrome, The Journal of Korean Medicine Ophthalmology and Otolaryngology Dermatology. 2012;25(2):61-7.
21. Lee SM, Lee CW, Jeon JH, Kim JH, Kim JI, Choi SM, Kim YI. Comparative study of the effect of acupuncture for dry eye syndrome according to difference of duration of treatment, The journal of Korean acupuncture & moxibustion medicine society. 2012;29(4):55-67.
22. Shin MS, Kin JI, Lee MS, Kim KH, Choi JY, Kang KW, Jung SY, Kim AR, Kim TH. Acupuncture for treating dry eye: a randomized placebo-controlled trial, Acta ophthalmologica. 2010;88:e328-e333.
23. Tong Lin, Lan Gong, Xiaoxu Liu, Xiaopeng Ma. Fourier-Domain Optical Coherence Tomography for monitoring the Lower Tear Meniscus in Dry Eye after Acupuncture Treatment, Evidence-based complementary and alternative medicine. 2015;2015:492150.
24. Apriani SA, Widya DK, Srilestari A, Susiyanti M. Acupuncture compared with 0.5% carboxymethyl cellulose for improving Schirmer 1 test and OSDI scores for treating dry eye in menopausal women, Journal of Physics. 2018;Conference Series1073(6):062034.
25. Dan Zhang, Yan Zhao, Yan-ting Yang, Yue Zhao, Dan-yan Wu, Xiao-xu Liu, Zheng Shi, Jue Hong, Jie Liu, Xiaoa-peng Ma. A mechanism study of electroacupuncture for dry eye syndrome by targeting conjunctival cytokine expression, Current Eye Research. 2020;45(4):419-27.



Appendix

Table 1. List of observational studies of Korean medicine treatment of dry eye

NO	Author (year)	Sample size (M/F)	Mean age(range)	Main treatment	Session & period	Outcome measurement	Main result	Adverse event
1	Jeon (2010)	50→32	47.4 (22-62)	acupuncture	3 times per week, total 12 times in 4 weeks	Dry eye symptoms OSDI Symptom score SIT BUT	1,2,3,4: improved (p<0.05) 5: no significant change	none
2	Chen (2012)	2 (1/1)	57 (65, 49)	acupuncture	20 mins, 1 time per week, total 6 times	Dryness Stinging sensation QoL	1,2: decreased 3: improved 4: M) stop, F) decreased	-
				Chinese herbal medicine	3 times per day	Use of artificial tears		
3	Lee (2010)	56→43 (14/29)	(20s-60s)	acupuncture	20 mins, 2-3 times per week, total 24 times	Symptom score The number of dry eye symptoms OSDI	1,2,3: improved (p<0.05)	-
4	Kang(2018)	6 (1/5)	50.3 (24,37,49,50,64,78)	pharmacopuncture	2 times per week, total 8 times	OSDI	1: improved	none
5	Kim(2019)	114 (42/72)	(19-80)	acupuncture	20 mins, 0~4 per week	OSDI	1: improved (p<0.001)	-
				herbal medicine	120 cc, 3 times after meal per day			

→: number of patients completed the treatment, OSDI: Ocular Surface Disease Index, SIT: Schirmer I test, BUT: Tear film break-up time, QOL: quality of life



Table 2. List of experimental studies of Korean medicine treatment of dry eye

NO	Author (year)	Sample size (M/F)	Mean age (range)	Main treatment	Intervention group (regime)	Control group (regime)	Outcome measurement	Main result	Adverse event
1	Shin(2010)	49→37	-	acupuncture	Verum ACP (20mins, 3 days per week, total 3 weeks/n=19)	Sham AC (3 days per a week, total 3 weeks/n=18)	OSDI VAS BUT SIT General assessment	1,2,3,4,5. I vs C: no statistical difference	none
2	Gong(2010)	44→42 (11/31)	I: 49.4±10.0 C: 40.68±12.16	acupuncture	ACP (20mins, 3 times per week, total 10 times in 3 weeks /n=20)	AT-Dextran 70 (1 drop 4 times per a day, total 3 weeks/n=22)	SSS SIT BUT RBS CFS Clinical efficacy	#At 3 weeks after treatment 1,2. I>C (p<0.05) 3. I vs C: no statistical difference 4. I: reduced, C: no change 6. I>C (p<0.05)	C: 2cases of foreign body sensation
3	Kim(2012)	150 (41/109)	I:47.95 C:46.05 (19-65)	acupuncture	ACP (20mins, 3 times per week, total 12 times in 4 weeks /n=75)	AT-0.5% sodium carboxymethylcellulose (at least 1 time per day, total 4 weeks/n=75)	OSDI VAS QOL SIT TFBUT	#At 8 weeks after treatment 1,2. I>C (p<0.05) 3,4. I vs C: no statistical difference 5. in right eye, I>C (p<0.05) *The efficacy of the treatment appeared slowly but lasted long.	I: 3cases of hematomas



NO	Author (year)	Sample size (M/F)	Mean age (range)	Main treatment	Intervention group (regime)	Control group (regime)	Outcome measurement	Main result	Adverse event
4	Liu(2013)	90 (60/30)	I:58(36-74) C:56(29-70)	acupuncture & chinese medicine	ACP (30mins, once every other day, total 3 courses in 90days/n=44) Chinese medicine - cool mist (15mins before acupuncture treatment, once every other day, total 3 courses in 90days/n=44)	AT-Sodium Hyaluronate eye drops (1-2 drops for each dose, 3 times a day , total 3 courses in 90days/n=46)	SIT DES symptom BUT Clinical efficacy	1,2. I>C(p<0.05) 3. I vs C: no statistical difference 4. I>C(p<0.01)	-
5	Lin (2015)	78 (except for SSDE patients)	LTD I:41 C:36 Non-SSDE I:46 C:47	acupuncture	A) ACP LTD-lipid tear deficiency (30mins, 3 times per week, total 4weeks/ n=9) B) ACP Non-SSDE-non sjogren syndrome dry eye (30mins, 3 times per week, total 4weeks/ n=26)	C)AT-Carboxymethylcellulose sodium eye drops LTD-lipid tear deficiency (4 times per day, total 4 weeks/ n=10) D)AT-Carboxymethylcellulose sodium eye drops Non-SSDE-non sjogren syndrome dry eye (4 times per day, total 4 weeks/ n=33)	TMH TMD TMA OSDI SIT TBUT CFS	1,2,3,4,5,6. I>C(p<0.05) 7. I vs C: no statistical difference	I: 2cases of petechia



NO	Author (year)	Sample size (M/F)	Mean age (range)	Main treatment	Intervention group (regime)	Control group (regime)	Outcome measurement	Main result	Adverse event
6	Liu(2017)	28 (-/28)	I:60.714±3.292 C:60.786±3.745	acupuncture & artificial tear	ACP & AT (3 times per week, total 8weeks/n=14)	AT(total 8weeks/n=14)	Scores of symptom OSDI Scores of sign TBUT SIT Protein analysis	1,2. I>C(p=0.000) 3,4,5. I vs C: no statistical difference	-
7	Tong(2018)	150 (34/116) →149	(40-85)	eye-drop, acupuncture, herbal medication	A) eye drop & ACP ED:4times per day AT:2 times per week/n=50 B) eye drop & HB ED:4times per day HB:2 times per day/n=49	C)eye drop-Systane ultra (4times per day/n=50)	SPEED NIBUT Conjunctival redness Tear cytokine CFS SIT Tear osmolarity	A>C (p<0.05), B,C: no statistical difference A<C (p<0.05), B,C: no statistical difference A>C (p<0.05) 4. Th1-cytokine tumour necrosis factor, Th2-sytokine interleukin 4 concentration: A>C (p<0.05), other cytokine: no statistical difference 5,6. A,B,C: no statistical difference 7. A>C, B>C (staining ↓)	none
8	Apriani(2018)	63 (-/63)	-	acupuncture, artificial tear	A) ACP-1time (20mins, total 1 times/n=21) B) ACP-2times (20mins, total 2 times/n=21)	eye drop-CMC(carboxy methyl cellulose 0.5%) (1 drop 4 time per day, total 7 days/n=21)	SIT OSDI	1,2. I vs C: no statistical difference	C: 1case of visual blur



NO	Author (year)	Sample size (M/F)	Mean age (range)	Main treatment	Intervention group (regime)	Control group (regime)	Outcome measurement	Main result	Adverse event
9	Dhaliwal(2019)	58→49 (10/39)	I:54±13(24-83) C:60±14(24-83)	-	True ACP -12 needles (45mins, 1 treatment on 2 consecutive days, total 2 session/n=24)	Sham ACP - 4 needles (45mins, 1 treatment on 2 consecutive days, total 2 session/n=25)	OSDI TBUT SIT Ocular surface grading Artificial tear application Frequency of eye closing DES symptom score	#At 6months after treatment I>C(p<0.05) . I vs C: no statistical difference 3,4,5,6.: I>C(p<0.05) 7. I vs C: no statistical difference	-none
10	Zhang(2019)	60 (-60)	I:54.28±6.18(50-56) C:53.96±8.68(50-56)	buddleja officinalis eye-drop, artificial tear	buddleja officinalis eye-drop & artificial tear-hypromellose 2019, Dextran 70 and Glycerol Eye drops (3 times per day, total 8 weeks/n=30)	artificial tear(3 times per day, total 8 weeks/n=30)	OSDI SIT FL score BUT HTM Tear protein	#At 8 weeks of therapy 1,2,3,4,5,6. I>C(p<0.05)	-
11	Gao (2016)	88 (55/33)	A:41.5±8.84 B:42.1±7.18 (18-70)	acupuncture & thread-embedding therapy	A) ACP & thread-embedding therapy AT: 30mins, once a day, total 24 times /n=44 Thread-embedding therapy: embedding for 8 times/n=44	B) ACP (30mins, once a day, total 24 times /n=44)	Symptom score(eye drying, foreign body sensation, burning sensation, photophobia, asthenopia) SIT BUT Clinical efficacy	Foreign body sensation: A,B no statistical change, Eyes drying, Burning sensation, Photophobia, Asthenopia: A>B (p<0.05) 2,3,4. A>B (p<0.05)	-



NO	Author (year)	Sample size (M/F)	Mean age (range)	Main treatment	Intervention group (regime)	Control group (regime)	Outcome measurement	Main result	Adverse event
12	Lee (2012)	92→75 (26/49)	(19-70)	acupuncture	A) ACP-12 times (30mins, 3 times per week / total 12times in 4weeks, n=32)	B) ACP-24 times (30mins, 3 times per week / total 24times in 8weeks, n=43)	Symptom score The number of dry eye symptoms OSDI	1. A<B (p<0.05) 2,3. A vs B: no statistical difference	-
13	Lee (2012)	11	-	acupuncture & Restasis & artificial tear	A) ACP & Restasis (acupuncure: 20mins, 1 time per week / total 3 times, Restasis: frequently)	B) ACP & AT (ReFresh, Kynex, Hyalein) acupuncure: 20mins, 1 time per week / total 3 times, artificial tears: frequently)	BUT SIT	ACP & Restasis 1,2. improved (p<0.05) ACP & AT 1,2. no statistical difference	-
14	Zang (2019)	-	(18-65)	Acupuncture	A)ACP (30mins, 3 times per week / total 12time)	B)EACP (30mins, 3 times per week / total 12time)	OSDI STI BUT	1. .decreased 2,3..A<B (p<0.01)	-

→: number of patients completed the treatment, ACP: acupuncture, EACP: electroacupuncture, ED: eye drop, HB: herbal medicine, AT: artificial tear, OSDI: Ocular Surface Disease Index, SIT: Schirmer I test, TFBUT/TBUT/BUT: Tear film break-up time, NIBUT: non-invasive tear break-up time, QOL: quality of life, VAS: visual analog scale, SSS: Symptoms, Signs and Total Score, RBS: Rose-Bengal staining, FL score/CFS: Corneal Fluorescein Staining, SPEED: Standard Patient Evaluation of Eye Dryness Questionnaire, DES: Dry eye syndrome, HTM/TMH: tear meniscus height, TMD: tear meniscus depth, TMA: tear meniscus area, LTD: lipid tear deficiency, Non-SSDE: non-Sjogren syndrome dry eye, I vs C: comparing results between intervention group and control group



Table 3. Traditional Korean medicine therapeutic methods of dry eye

Classification		Acupoint/ Herbal medicine
Acupuncture	Normal Acupuncture	攢竹 [BL2] 10, 睛明 [BL1] 8, 風池 [GB20] 7, 絲竹空 [TE23] 4, 陽白 [GB14] 6, 承泣 [ST1] 5, 合谷 [LI4] 6, 四神聰 EX1] 5, 四白 [ST2] 5, 太沖 [LR3] 4, 三陰交 [SP6] 4, 天府 [LU3] 3, 光明 [GB37] 3, 瞳子膠 [GB1] 3, [Ear-目2] 3*, [眼下(E2)] 3*, 上星 [GV23] 2, 太谿 [KI3] 2, 太陽 [EX5] 2, 太白 [SP3] 1, 太淵 [LU9] 1, 魚際 [LU10] 1, 少府 [HT8] 1, 神門 [HT7] 1, 曲池 [LI11] 1, 肝俞 [BL18] 1, 腎俞 [BL23] 1, 印堂 [EX3] 1, 商陽 [LI1] 1, 二間 [LI2] 1, 魚腰 [EX4] 1, [Between LI1 and LI2] 1*, [Ear-Salivary gland 2] 1*, [Ear-Point zero] 1*, [Ear-目1] 1*, [奪命] 1*, [Extra-Duomingxue] 1*
	Electroacupuncture	攢竹 [BL2], 太陽 [EX5], 絲竹空 [TE23], 四白 [ST2], 風池 [GB20], 百會 [GV20], 合谷 [LI4], 足三里 [ST36], 光明 [GB37], 三陰交 [SP6], 太沖 [LR3]
	Thread-embedding therapy	百會 [GV20], 承泣 [ST1], 攢竹 [BL2], 風池 [GB20], 太陽 [EX5], 絲竹空 [TE23], 三陰交 [SP6], 足三里 [ST36], 內關 [PC6], 太沖 [LR3], 肺俞 [BL13], 合谷 [LI4], 豐隆 [ST40], 脾俞 [BL20], 肝俞 [BL18], 腎俞 [BL23]
	Pharmacopuncture	上脘 [CV13], 中脘 [CV12], 下脘 [CV10], 鳩尾 [CV15], 關元 [CV4], 天樞 [ST25]
Herbal medicine	Herbal decoction	濟生腎氣丸 Jesaengsingi-hwan, 一貫煎 Ilgwanjeon, 加味逍遙散 Gamisoyo-san, 杞菊地黃丸+甘露飲 Gigukjihwang-hwan + Gamno-eum, 仁目湯 Inmok-tang, 丹蔘 Salviae Miltiorrhizae Radix, 女貞子 Ligustri Lucidi Fructus, 枸杞子 Lycii Fructus, 菊花 Chrysanthemi Flos, 穀精草 Eriocauli Herba, 牛膝 Achyranthis Radix, 防風 Saposhnikovia Radix, 鉤藤 Uncariae Ramulus cum Uncis, 黃連 Coptidis Rhizoma, 砂仁 Amomi Fuctus, 木賊 Equiseti Hiemalis Herba
	Herbal granules	密蒙花 Buddlejae Flos, 枸杞子 Lycii Fructus, 菊花 Chrysanthemi Flos, 陳皮 Fraxini Cortex, 鬼針草 Bidentis Herba, 水片 Borneolum

*For the extraordinary points, they were written without abbreviation.

