J Acupunct Res 2022;39(3):170-181

Journal of Acupuncture Research

Journal homepage: http://www.e-jar.org

Review Article

Effectiveness of Electroacupuncture in Patients with Chronic Fatigue Syndrome: A Systematic Review and Meta-analysis

Jaewoo Yang [1], Donghoon Shin [1], Jihoon Oh [1], Jinwoong Lim [2,*]

1 Department of Acupuncture and Moxibustion, Mokhuri Neck and Back Hospital, Seoul, Korea
2 Department of Acupuncture and Moxibustion, Wonkwang University Gwangju Korean Medicine Hospital, Gwangju, Korea

Article history:
Submitted: May 30, 2022
Revised: June 28, 2022
Accepted: July 13, 2022

Keywords:
chronic fatigue syndrome, electroacupuncture, meta-analysis, systematic review

https://doi.org/10.13045/jar.2022.00143
pISSN 2586-288X eISSN 2586-2898

ABSTRACT

This review evaluated the efficacy of electroacupuncture (EA) for chronic fatigue syndrome. Randomized controlled trials (RCTs) using EA as an intervention for patients with chronic fatigue syndrome were identified in 6 databases (PUBMED, EMBASE, CNKI, J-STAGE, KMBASE, OASIS). Fatigue indicators were used as the primary outcome measures. The quality-of-life index, efficiency rate, and level of pain were used as secondary outcome measures. There were 408 patients from seven RCTs included in this study. Meta-analysis showed that EA was significantly associated with fatigue relief compared with the control group (n = 141 SMD = −1.55, 95% CI: −2.58 – −0.52, p = 0.003, I^2 = 92%). In addition, EA had a statistically significant improvement in quality of life compared with the control group (n = 176, SMD = −2.29, 95% CI: −3.68 – −0.90, p = 0.001, I^2 = 96%). One study reported ten cases of bleeding, however, no serious adverse events were reported in any of the included studies. This review determined that EA may have a greater clinical effect than the control group for fatigue relief and improved quality of life. However, there were several risks of bias identified. Not all of the RCTs accurately reported the research method, all studies were conducted in 1 country (China), and the number of studies included were small.

Introduction

Chronic fatigue syndrome (CFS) is characterized by continued fatigue for 6 months or more which is not explained by other underlying disorders. Typical symptoms include insomnia, amnesia, musculoskeletal pain, and various neuropsychiatric symptoms [1]. CFS is a syndrome which was defined by the Centers for Disease Control and Prevention (CDC) in the United States in 1988 [2]. The prevalence of CFS has been increasing and may be due to lifestyle changes in modern society. Although this syndrome is not directly linked to fatal consequences, long-lasting fatigue and pain may have major impacts on physical and mental health.

A study by Wesley in 1995, reported that the prevalence rate of CFS of the World ranged from 0.8% to 1.8%, but only 12% of patients were aware that their symptoms may be caused by CFS [3]. Moreover, in 2022, the mechanisms and treatments for CFS are yet to be elucidated. Diagnosis is based upon ruling out other conditions and treatment aims to relieve how the individual is affected. Treatment with complementary and alternative medicine (CAM) is seen as a potential treatment. In the 2015 there was a review of 35 studies of CFS, but there were limitations due to the size of the population for each therapy and the quality of the studies [4]. Valid treatments used for CFS in these reviewed studies included cognitive behavioral therapy, immunoglobulin, valganciclovir, galantamine, inosine pranobex, fluoxetine, and CAM [5]. Various reviews of CAM as a treatment for CFS have

***Corresponding author.** Jinwoong Lim
Department of Acupuncture and Moxibustion, Wonkwang University Gwangju Korean Medicine Hospital, 1140-23, Hoejae-ro, Nam-gu, Gwangju 61729, Korea
E-mail: jwlim0123@gmail.com
ORCID: Jaewoo Yang https://orcid.org/0000-0001-6613-8975, Donghoon Shin https://orcid.org/0000-0002-1458-2086, Jihoon Oh https://orcid.org/0000-0002-9527-8384, Jinwoong Lim https://orcid.org/0000-0003-2080-9432

been published. However, it appears that more rigorous RCTs, than those reviewed in 2011 (26 RCTs) by Terje et al [6] where the effectiveness of CAM for CFS provided limited evidence of success due to the small sample size for each therapy and high risk of bias, are necessary. Acupuncture, an important treatment within CAM, has been studied as a treatment for CFS. Wang et al [7] conducted a systematic review of acupuncture for CFS in 2009, Kim et al [8] and Zhang et al [9]. The conclusions from all 3 studies were that more rigorous RCTs are required.

In this review, studies were selected based upon electroacupuncture (EA) treatment of CFS. So far, there have been no reviews on the correlation between CFS and EA. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that have examined the overall effect of EA compared with conventional acupuncture and Herbal medicine treatments.

Materials and Methods

Study design

This study was a systematic review of RCTs that compared the effects of EA in patients with persistent fatigue (≥ 6 months) due to CFS, as defined by the CDC. This study was conducted according to the 2020 systematic literature review reporting guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analysis. The protocol for this study was registered with PROSPERO (the international register of systematic reviews; registration no.: CRD42022328988) [10].

Search strategy

A number of databases were searched with the aim of reducing language bias. Studies in English, Japanese, Chinese, and Korean were included. 2 English language databases [MEDLINE via PubMed, Excerpta Medica Database (EMBASE)], a Chinese database [China Knowledge Infrastructure for Chinese studies (CNKI)], a Japanese database [Japan Science and Technology Information Aggregator Electronic database (J-STAGE)], and 2 Korean databases [Korea Medical Database (KMbase)], Oriental Medicine Advanced Searching Integrated System (OASIS) were searched for studies published up to April 2022.

A search strategy was established to include all studies covering EA and CFS. The search terms varied according to each database (Table 1).

Eligibility criteria

Types of studies

In this study, related RCTs were included as targets for analysis. Cohort studies, case reports, observational studies, qualitative studies, case controls, and in vivo and in vitro studies, reviews, i.e., not RCTs, were excluded. In addition, studies where the original text was not available were also excluded.

Types of patients

In accordance with the diagnostic criteria of the 1994 CDC definition of CFS, patients diagnosed with CFS were included, and studies on idiopathic chronic fatigue were excluded. The patients' race, age, sex, period of morbidity, and main symptoms were recorded without limitations.

Types of interventions

Studies where treatment methods were described as EA or electrical stimulation applied with acupuncture were included in this review (therefore, electrical acupoint stimulation studies were included). All EA and treatment methods were included except

Table 1. Search Strategies for Each Database.

1. PubMed	#1.Search: (("electroacupuncture"[MeSH Terms] OR ("electroacupuncture"[MeSH Terms] OR "electroacupuncture"[All Fields] OR "electroacupuncturing"[All Fields]) OR "electro-acupuncture"[All Fields] OR "acupoint electrical stimulation"[All Fields])) #2.Search: (("fatigue syndrome, chronic"[MeSH Terms]) OR ("fatigue" [All Fields] AND "syndrome"[All Fields] AND "chronic"[All Fields]) OR "chronic fatigue syndrome"[All Fields] OR ("chronic"[All Fields] AND "fatigue"[All Fields] AND "syndrome"[All Fields])) #3.#1 AND #2
2. EMBASE	#1.('electroacupuncture'/exp OR electroacupuncture OR 'electro acupuncture'/exp OR 'electro acupuncture' OR 'acupoint electrical stimulation') AND ('fatigue syndrome, chronic'/exp OR 'fatigue syndrome, chronic' OR (('fatigue'/exp OR 'fatigue') AND ('syndrome'/exp OR 'syndrome') #2.('syndrome'/exp OR 'syndrome') AND 'chronic') OR 'chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome' OR ('chronic' AND ('fatigue'/exp OR 'fatigue') AND ('syndrome'/exp OR 'syndrome'))) #3.#1 AND #2
3. CNKI	(SU=electroacupuncture OR SU=electro-acupuncture OR SU="acupoint electrical stimulation") AND ((SU="fatigue syndrome, chronic") OR (SU="fatigue" AND SU="syndrome" AND "chronic") OR SU="chronic fatigue syndrome" OR (SU="chronic" AND SU="fatigue" AND SU="syndrome"))
4. J-stage	(electroacupuncture OR electro-acupuncture OR "acupoint electrical stimulation") AND (("fatigue syndrome, chronic") OR ("fatigue" AND "syndrome" AND "chronic") OR "chronic fatigue syndrome" OR ("chronic" AND "fatigue" AND "syndrome"))
5. Korean databases (KMBASE, OASIS, KISS, RISS)	"All = CFS" OR "All = chronic fatigue syndrome" OR "All = chronic fatigue syndrome (in Korean)" AND All = "acupuncture"

Auricular EA, which stimulates points in the ear without using acupoints. They were included without considering the shape of acupuncture, the degree and intensity of electrical stimulation, and the duration and frequency of treatment.

Types of outcome measures

To evaluate the effectiveness of the treatment, studies that contained at least one of the following outcomes were included. The most common symptom of CFS was extreme fatigue, therefore, indicators of fatigue were selected as the primary outcome measure using the fatigue severity scale (FSS), fatigue assessment instrument (FAI), and the fatigue scale-14 (FS-14). Indicators that can show the quality of life (QoL) of patients with CFS were selected as the secondary outcome measures including the Somatic and Psychological Health Report-34 items (SPHERE), the WHO Quality of Life-BREF (WHOQOL-BREF), the total effective rate (TER), and the visual analog scale.

Data extraction process

2 independent researchers extracted the information according to the inclusion/exclusion criteria. After excluding overlapping studies, titles and abstracts were selected. Eligible studies were selected based on the intervention, diagnostic criteria, outcome measures, and randomization method detailed in the full body of the text. If a disagreement occurred in the selection process, a 3rd researcher was asked for their opinion when necessary.

The following information was extracted from the selected studies: literature included in the study, sample size, age, sex, season duration, primary outcome measurement, secondary outcome measurement, and adverse events. In addition, the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines [11] were used to collect data on the interventions (number of participants, age, sex, morbidity period), interventions (number of interventions, acupoint, treatment frequency, and duration), and control interventions (number of controls, treatment, and duration). Two researchers independently conducted the data collection process. If a disagreement occurred in the data collection process, a 3rd researcher was asked for their opinion.

Risk of bias assessment

Two researchers independently evaluated the risk of bias (RoB) in the selected randomized controlled clinical studies. The RoB assessment considered 7 items (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective outcome reporting, and other potential biases) according to Cochrane's RoB tool [12]. Each item was categorized as having a high, low, or unclear risk. If the opinions of the two researchers were inconsistent, an agreement was made through discussion. If a disagreement occurred in the RoB assessment process, a 3rd researcher was asked for their opinion.

Data synthesis and analysis

Meta-analysis was used to compare the effects of treatment intervention in the selected studies. Data synthesis was performed using RevMan Version 5.3.0 for Windows. When the outcome was on the same scale, continuous variables were analyzed using the mean difference (MD) based on a 95% confidence interval (CI). When the scales were not the same, the standardized MD (SMD) was used for the analysis. Heterogeneity analysis was performed using Higgins' heterogeneity test and chi-square test.

Since the RCTs included in this review did not consider factors such as season, type of need, fixed or selected points for symptoms, intensity, frequency, and treatment period, data synthesized from these studies considered their reliability.

Using GRADEpro software, the quality of evidence of each study included in the meta-analysis was evaluated, and a summary table was constructed (Tables 2 and 3) [13]. Of note, publication bias was not evaluated because the Cochrane Handbook for Systematic Reviews of Interventions states that when there are fewer than ten studies included in the analysis, publication bias need not be performed [12].

Results

Study selection

As a result of searching domestic and foreign databases, 2 studies were identified from PubMed, 14 from EMBASE, 34 from CNKI, 98 from J-STAGE, 204 from KMBASE, and 2 from OASIS.

A total of 278 articles were identified, excluding overlapping articles. In total, 262 studies were excluded based on their titles and abstracts. 11 studies were not related to CFS or EA, 124 were not RCTs, and 7 were study protocols. A total of 262 studies were excluded. 9 of the 16 remaining studies were excluded after reviewing the full text. 2 studies in which EA treatment was used in both the control and experimental groups were excluded. 3 articles were excluded because they described the same study, 3 used unsuitable outcome measures (only vital signs), and 2 used interventions different from the inclusion criteria. Finally, 7 studies were included in the systematic review, and 6 were analyzed in the meta-analysis (Fig. 1).

Study information

There were 408 patients with CFS from seven RCTs [14-20] who were treated with EA were included in this review (Table 4). A total of 206 patients were assigned to the EA experimental group, and 202 to the control group. The RCTs included in this review were conducted between 2006 and 2019.

All 7 studies [14-20] were conducted using the diagnostic criteria revised by the CDC in 1994. The RCTs were conducted in a 2-arm parallel trial (except for the study by Li et al [16], which did not detail the sex and age of the participants), 136 males and 212 females were included. The average age of the patients was 38.18 years, and the duration of morbidity was at least 7 months. 2 dropouts were reported in one of the seven studies [18], and no dropouts were

Table 2. GRADE Table of Included Studies: Fatigue.

Certainty assessment							No. of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EA	control	Relative (95% CI)	Absolute (95% CI)	
Fatigue											
5	Randomized trials	Serious*,†,‡	Serious§;	Not serious	Not serious	None	141	157	-	SMD 1.54 lower (2.57 lower to 0.52 lower)	⊖⊖○○ Low
Fatigue - EA vs Acu (FSS)											
2	Randomized trials	Very serious*,†,‡	Not serious	Not serious	Not serious	None	76	93	-	SMD 1.99 lower (4.26 lower to 0.28 higher)	⊖○○○ Very Low, ‖
Fatigue - EA vs sham EA (FSS)											
2	Randomized trials	Serious†,‡	Not serious	Not serious	Not serious	None	35	34	-	SMD 1.54 lower (2.97 lower to 0.1 lower)	⊖⊖○○ Low, ‖
Fatigue - EA+H-med vs H-med (FAI)											
1	Randomized trials	Serious†,‡	Not serious	Not serious	Not serious	None	30	30	-	SMD 0.74 lower (1.27 lower to 0.22 lower)	⊖⊖○○ Low, ‖

* One study has high risk of selection bias.
† High risk of performance bias.
‡ Unclear risk of bias in several domains.
§ Synthesis between studies with different controls.
‖ Small number of participants of meta-analysis.
CI, confidence interval; SMD, standardised mean difference.

reported in the other studies.

4 studies [14-17] compared EA with conventional acupuncture, and 1 study [17] compared EA with moxibustion (with oryzanol) and routine acupuncture. 2 studies [18,19] compared EA with sham EA where the acupuncture was placed at a distance and electrical stimulation was used, and one study [20] compared a group that received EA with herbal medicine and herbal medicine alone.

4 studies designated the FSS score as the primary outcome measure [14,15,18,19], 1 designated the FAI [20], 1 designated the FS-14 [17], and 1 designated the TER [16]. Regarding the secondary outcomes, 5 studies designated the SPHERE [14,15,17-19] and 1 designated the WHOQOL-BREF [20]. 1 study [16] had only 1 outcome measure which was the TER. In 1 study [17], 2 people dropped out of the control group, and the reason for the dropout was not stated. No dropouts were reported in the other studies.

Interventions

Using the STRICTA guidelines [11], the matters related to the intervention of the 7 RCTs patients are shown in Table 5.

Treatment period and frequency

4 studies [14,15,17,20] treated patients for four weeks, with the sessions conducted once a day [17], 5 times a week [14], 3 times a week [20], and 2 times a week [15]. In 2 studies [16,19], treatment was performed for ten days, with the sessions conducted once a day [19], and once every 3 days [16]. In another study [18], ten sessions were conducted over 12 days.

Acupoint

The most frequently used acupoint was ST36 [15-16,18-20], which was used in 5 studies. CV4 [14-16,20], CV8 [14,15,17,20], and BL23 [15,16,18,19] were used in 4 studies. 5 studies used the CV meridian [14-17,20] and CV meridian acupoints.

When studies were classified by the control group, each study showed homogeneity in the treatment acupoints, and CV meridian acupoints were used in 4 studies [14-17] where the control was conventional acupuncture.

CV4 [14-17] was used in 3 studies, and CV8 [14,17] and ST36 [15,16] were used in 2 studies. In 2 studies [18,19] where the control group was sham EA, ST36 and BL23 were used as acupoints to show similarities.

In 3 studies [15,16,20], the acupoints were selected according

Table 3. GRADE Table of Included Studies: QoL.

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EA	control	Relative (95% CI)	Absolute (95% CI)	
QoL											
6	Randomized trials	Serious*,†,‡	Serious§	Not serious	Not serious	None	176	172	-	SMD 2.29 lower (3.67 lower to 0.9 lower)	⊖⊖○○ Low
QoL - EA vs Acu (SPHERE)											
3	Randomized trials	Very serious*,†,‡	Not serious	Not serious	Not serious	None	111	108	-	SMD 3.39 lower (6.38 lower to 0.41 lower)	⊖○○○ Verylow, ‖
QoL - EA vs Sham EA (SPHERE)											
2	Randomized trials	Serious†,‡	Not serious	Not serious	Not serious	None	35	34	-	SMD 1.3 lower (2.88 lower to 0.28 higher)	⊖⊖○○ Low, ‖
QoL - EA+H-med vs H-med (WHOQOL-BREF)											
1	Randomized trials	Serious†,‡	Not serious	Not serious	Not serious	None	30	30	-	SMD 1.15 lower (1.7 lower to 0.6 lower)	⊖⊖○○ Low, ‖

* One study has high risk of selection bias.
† High risk of performance bias.
‡ Unclear risk of bias in several domains.
§ Synthesis between studies with different controls Although there is a heterogeneity, they have same effect for alleviating fatigue.
|| Small number of participants of meta-analysis.
CI, confidence interval; SMD, standardized mean difference.

to the patient's symptoms. 1 study [16] suggested the standard treatment should include BL23 when insomnia was present and GB34 when muscle pain was present. 3 studies [17-19] recorded acupuncture points where electrical stimulation was provided, but other studies [14-16, 20] did not mention this.

Treatment method

Regarding the length of the needle used, 1-1.5 cun was used in 1 study [15,18,20], 2 cun was used in 1 study [19], and a 0.30 × 0.40 needle was used in 1 study [16]. There was no mention of the length of the needle used in 2 studies [14,17].

As for the needle depth, insert needle until "de qi" is experienced was used as the standard in 6 studies [14-16, 18-20]. In 1 study [17], the exact depth and direction of the insert (15 mm parallel to the ear canal) were recorded. The intensity of EA was set according to the patient's tolerance level in 6 studies [15-20], and there was no mention in 1 study [14]. The frequency was different in all studies, 3 Hz [14], 4/20 Hz [17], and 20-100 Hz [18] were used, and in 4 studies [15,16,19,20], there was no mention of the frequency used. In 5 studies [14-17,20], the treatment time was 30 minutes, and in 2 studies [18,19] it was 20 minutes.

Risk of bias

The RoB was evaluated using Cochrane's RoB tool for the 7 RCTs. Revman 5.3.0 is shown in Figs. 2 and 3.

Random sequence generation

In 1 study [14], the opaque envelopes method of randomization approved by Huzhou Hospital ethics commission committee was used. In 2 studies [17,20], randomization was performed using a random number table. Therefore, the RoB for random sequence generation was rated as "low" for these studies. There was no mention of the randomization method in 3 studies [16,18,19], so it was evaluated as "unclear" RoB. In 1 study [15], the RoB was evaluated as "high" because it was mentioned that the assignment was made through visit order.

Allocation concealment

In 2 studies [14,17], the RoB for allocation concealment was evaluated as "low" because an independent 3rd party concealed the allocation, and the remaining 5 studies [15,16,18,19,20] did not mention the concealment of the allocation order. Therefore, the RoB in those studies was evaluated as "unclear."

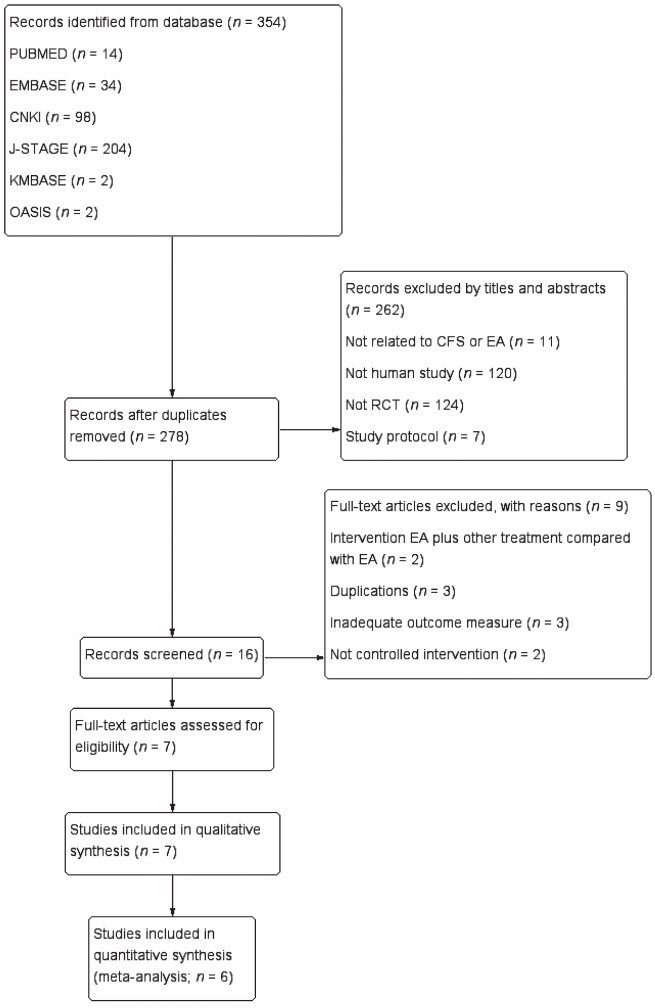

Fig. 1. Flow diagram of the study selection process.

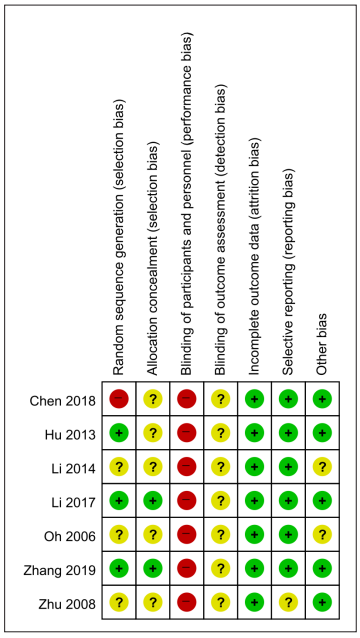

Fig. 2. Risk of bias summary.

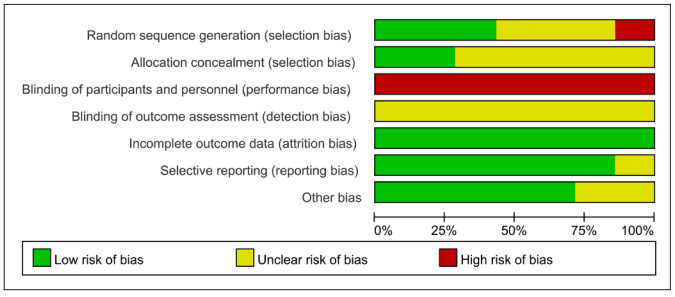

Fig. 3. Risk of bias graph.

Blinding of participants and personnel

Due to the nature of EA, it is difficult to blind the operator and patient. Blinding was not performed in all 7 studies [14-20], and the RoB was evaluated as "high."

Blinding of outcome assessment

In 7 studies [14-20], the risk was evaluated as "uncertain" because there was no mention of the blinding of the evaluators.

Incomplete outcome data

In 1 study [18], the risk was evaluated as "unclear" because there was no reason presented for the missing value. The RoB for incomplete outcome data was rated as "low" in the other 6 studies because there was no missing data.

Selective reporting

All 7 studies [14-20] reported all expected results in the experimental design of their study. Therefore, the RoB for selective reporting was rated as "low."

Other bias

Although reports on baseline partisans were omitted in 2 studies [16,19], the RoB was evaluated as "unclear" for other bias because the *p* value between the 2 groups showed less heterogeneity. In all five studies [14-19,20], the RoB was evaluated as "low" because there was no claim that the design was potentially biased.

Effectiveness of intervention

Fatigue

Meta-analysis was conducted by synthesizing 5 studies [14,15, 18-20] using the indicators of the level of fatigue including the FSS and the FAI. 2 studies [14,15] compared EA with conventional acupuncture, 1 study [18,19] compared EA with sham EA, and 1 study [20] compared EA with herbal medicine and herbal medicine alone were analyzed when categorized into small groups, and then the total results were analyzed again (Fig. 4).

SMD was used to analyze the different indicators. The random-effects model was used to show whether there was a lot of

Table 4. Result of Included Studies.

Author (year)	Sample size (included ->analyzed) Diagnosis	TG fender and mean age (mean±SD) CG gender and mean age (mean±SD)	TG disease duration (mo) (mean± SD) CG disease duration (mo) (mean± SD)	Treatment intervention	Control intervention	Outcome measure	Result*	Adverse event
EA VS Conventional Acupuncture								
Li (2017) [14]	89 (46/43→46/43) 1994 CDC	M/F = 18/28 39 ± 10 M/F = 17/26 38±9	13.6 ± 6.9 14.0 ± 6.6	EA	Acupuncture	1) FSS 2) SPHERE	(T/C, Baseline, 4 wk) 1) 40.41 ± 3.61→24.41 ± 3.62 (p < 0.001)/ 39.02 ± 5.28→38.14 ± 4.78 (p < 0.001) 2) 25.96 ± 2.76→12.74 ± 2.27 (p < 0.001)/ 25.07 ± 2.44→24.19 ± 1.06 (p < 0.001)	None
Chen (2018) [15]	60 (30/30) 1994 CDC	M/F = 11/19 45.03 ± 5.12 M/F = 10/20 44.68 ± 5.23	22.36 ± 7.02 23.12 ± 6.89	EA	Cat gut Acupuncture	1) FSS 2) SPHERE 3) TER	(T/C, Baseline, 4 wk) 1) 51.70 ± 11.37→35.07 ± 7.54 (p >0.05)/ 52.73 ± 11.75→41.15 ± 6.87 (p > 0.05) 2) 34.54 ± 4.11→10.55 ± 2.41 (p > 0.05)/ 35.22 ± 4.85→12.36 ± 2.63 (p > 0.05) 3) 90.00%/86.67% (p > 0.05)	Not reported
Li (2014) [16]	60 (30/30→30/30) 1994 CDC	Not disclosed (25-50) Not disclosed (25-50)	Not disclosed (at least 7 mo) Not disclosed (at least 7 mo)	EA	Acupuncture	1) TER	(T/C, Baseline, 10d) 1) 93.33%/83.33% (p < 0.5)	Not reported
Zhang (2019) [17]	70 (35/35→35/35) 1994 CDC	M/F = 17/18 38.22±9.25 M/F = 16/19 37.56 ± 9.91	11.94 ± 5.19 37.56 ± 9.91	EA+Mox	Acupuncture+ W-med	1) FS-14 2) SPHERE 3) PSQI 4) IL-6 5) IFN-γ	(T/C, Baseline, 4wk) 1) 5.72 ± 0.91→1.57 ± 0.42 (p < 0.05)/ 5.85 ± 0.83→3.34 ± 0.47 (p < 0.05; physical) 4.97 ± 0.77→1.24 ± 0.32 (p < 0.05)/ 4.56 ± 0.69→2.34 ± 0.41 (p < 0.05; mental) 2) 25.45 ± 5.22→9.02 ± 1.95 (p < 0.05)/ 24.86 ± 5.49→16.69 ± 2.69 (p < 0.05) 3) 17.22 ± 3.21→5.05 ± 1.83 (p < 0.05)/ 16.89 ± 3.97→10.76 ± 2.09 (p < 0.05) 4) 45.61 ± 5.91→25.57 ± 4.19 (p < 0.05)/ 46.88 ± 6.02→36.34 ± 4.40 (p < 0.05) 5) 49.98 ± 5.77→27.20 ± 3.82 (p < 0.05)/ 46.88 ± 6.02→37.52 ± 4.43 (p < 0.05)	Not reported
EA VS non-acu point electric stimulation								
Zhu (2008) [18]	60 (30/30->30/28) 1994 CDC	M/F = 6/24 38.50 ± 7.89 M/F = 10/20 37.67 ± 9.85	15.30 ± 5.72 16.70 ± 5.43	EA	Non-acu point electric stimulation	1) FSS 2) SPHERE 3) VAS	(T/C, Baseline, 3 mo) 1) 46.93 ± 5.65→25.60 ± 5.06 (p < 0.001)/ 45.77 ± 5.35→38.47 ± 6.64 (p < 0.001) 2) 19.77 ± 3.35→7.83 ± 2.84 (p < 0.001)/ 19.47 ± 2.89→14.77 ± 3.92 (p < 0.001) 3) 59.33 ± 14.13→ 31.00 ± 10.62 (p < 0.01)/ 56.67 ± 11.55→ 42.33 ± 10.06 (p < 0.01)	Not reported

Table 4. (continued).

Author (year)	Sample size (included ->analyzed) Diagnosis	TG fender and mean age (mean±SD) CG gender and mean age (mean±SD)	TG disease duration (mo) (mean± SD) CG disease duration (mo) (mean± SD)	Treatment intervention	Control intervention	Outcome measure	Result*	Adverse event
EA VS non-acu point electric stimulation								
Oh (2006) [19]	9 (5/4→5/4) 1994 CDC	M/F = 1/4 36.60 ± 6.84 M/F = 6/24 35.75 ± 5.12	Not disclosed (at least 7 mo) Not disclosed (at least 7 mo)	EA	Non-acu point electric stimulation	1) FSS 2) SPHERE	(T/C, Baseline, 3 mo) 1) 50.20 ± 8.82→31.00 ± 9.62 (p <0.05)/ 44.75 ± 10.34→40.00 ± 14.78 (p <0.05) 2) 21.00 ± 3.08→13.60 ± 9.29 (p <0.05)/ 19.00 ± 4.54→16.75 ± 3.86 (p < 0.05)	Not reported
EA VS Conventional treatment								
Hu (2013) [20]	60 (30/30→30/30) 1994 CDC	M/F = 12/18 37.36 ± 8.55 M/F = 13/17 37.20 ± 6.93	38.27 ± 8.73 39.30 ± 7.55	EA+H-med	H-med	1) FAI 2) WHOQOL-BREF	(T/C, Baseline, 10 days) 1) 145.53 ± 9.96→78.67 ± 9.52 (p < 0.01)/ 147.37 ± 8.37→86.33 ± 10.78 (p < 0.01) 2) 78.03 ± 8.62→99.77 ± 7.86 (p < 0.01)/ 75.80 ± 9.56→84.57 ± 16.74 (p < 0.01)	10 bleeding

* The inequality sign is the favourable of the result value.
† All p values are comparisons between I/C.
C, control; CDC, Centers for Disease Control and Prevention; CG, control group; F, female; FS-14, fatigue scale-14; FSS, fatigue severity scale; H-med, herbal medicine; M, male; PSQI, Pittsburgh Sleep Quality Index; SPHERE, The Somatic and Psychological Health Report-34 items; T, treatment; TER, total effective rate; TG, treatment group; VAS, visual analogue scale; WHOQOL-BREF, WHO Quality of Life-BREF; W-med, Western medicine.

Table 5. Details of Electroacupuncture Interventions.

Author (year)	Treatment period	Treatment Frequency	Acupoint	Details of needling	Details of EA	Needle retaining time
Li (2017) [14]	4 wk	5 x/wk	GV 14, GV 4, CV 8, CV 4	Insert needle until de qi	Fre 100/2 Hz 14±2 mA	30 min
Chen (2018) [15]	4 wk	2 x/wk	CV17, CV6, CV4, ST36, BL13, BL18, BL20, BL23, Select 10 points at a time from the above acupoints	1~1.5 cun needle, insert needle until de qi	Fre: 3Hz Int: according to the patient's tolerance level	30 min
Li (2014) [16]	10 d	1 x/3 d	CV4, ST36, PC6, EX-HN 5 BL23 (if have insomnia), GB34 (if pain at muscle)	0.30 x 0.40 needle, insert needle until de qi	Int: according to the patient's tolerance level	30 min
Zhong (2019) [17]	4 wk	1 x/d	CV8 (EA), TE17 (EA)	TE17: insert 15 mm parallel to ear canal	Int: according to the patient's tolerance level	30 min
Zhu (2008) [18]	12 d	10 x/12 d	ST36 (EA), BL23 (EA)	1~1.5 cun needle, insert needle until de qi	Fre: 4/20Hz Int: according to the patient's tolerance level	20 min
Oh (2006) [19]	10 d	1 x/d	ST36 (EA), BL23 (EA)	2 cun needle, insert needle until de qi	Fre: 20-100Hz Int: according to the patient's tolerance level	20 min
Hu (2013) [20]	4 wk	3 x/wk	1) CV 4, EX-HN 1 BL15, BL17, BL18, BL20, 2) GV 4, CV 6, CV 4, ST 36, LI 4, LR3 Select 1) or 2)	1~1.5 cun needle, insert needle until de qi	Int: according to the patient's tolerance level	30 min

AP, acupoint; EA, electroacupuncture; Fre, frequency; Int, intensity; Loc, location; NR, not reported.

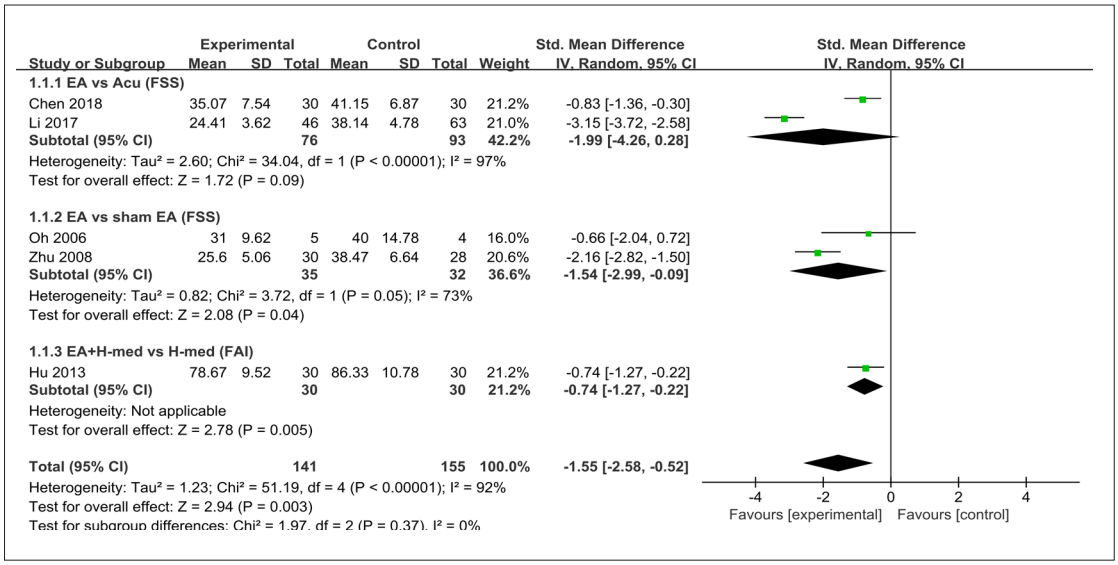

Fig. 4. Fatigue: Electroacupuncture versus control group.

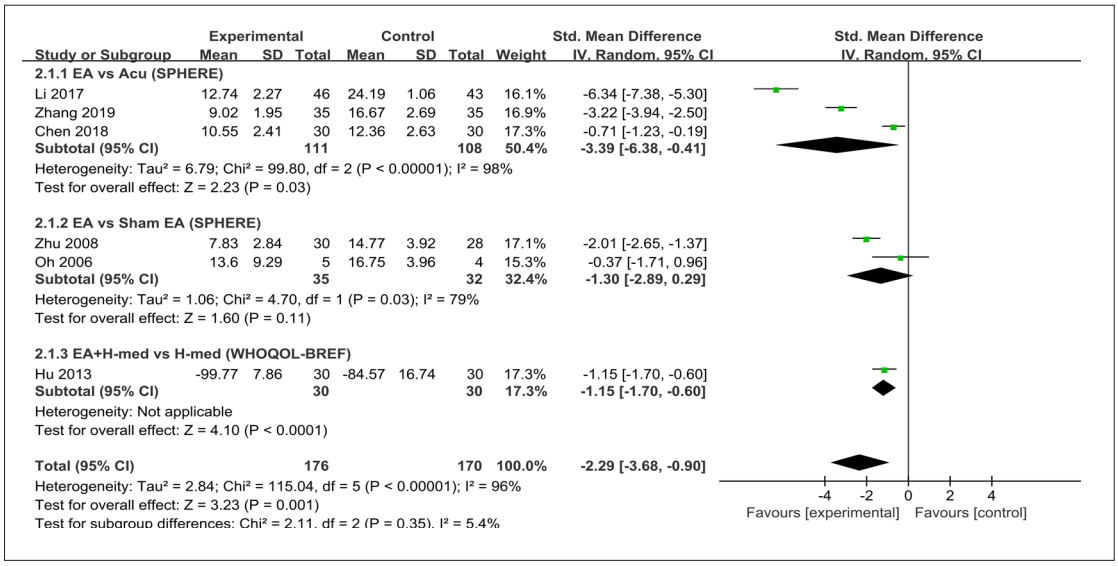

Fig. 5. Quality of Life: Electroacupuncture versus control group.

heterogeneity in the study results due to the lack of consistency in the design of the study and the intervention.

In an analysis that compared EA with Acupuncture, the intervention group had a lower FSS index than the control group. The heterogeneity of the 2 studies was high (I^2 = 97%), and there were no statistically significant differences between the intervention and control groups (SMD = −1.99, 95% CI: −4.26–0.28, p = 0.09, I^2 = 97%).

The intervention group showed a greater decrease in the FSS compared with the control group. The heterogeneity of the 2 studies was high at I^2 = 73%, and the intervention group showed a statistically significant reduction in fatigue compared with the control group. (SMD = −1.54, 95% CI: −2.99 – −0.09, p = 0.04, I^2 = 73%)

Comparing EA with herbal medicine and herbal medicine alone, the results of this study showed a significantly lowered FAI index in the intervention group compared with the control group (SMD = −0.74, 95% CI: −1.27–−0.22, p = 0.005, I^2 = Not applicable).

The analysis of the three groups showed that EA significantly reduced fatigue compared with the control group. The heterogeneity of all the studies was high at I^2 = 92%, but between small groups, it was low, resulting in I^2 = 0%. In the quality evaluation using the GRADE tool, the quality of the meta-analysis was downgraded due to the RoB and indirect factors (Table 2).

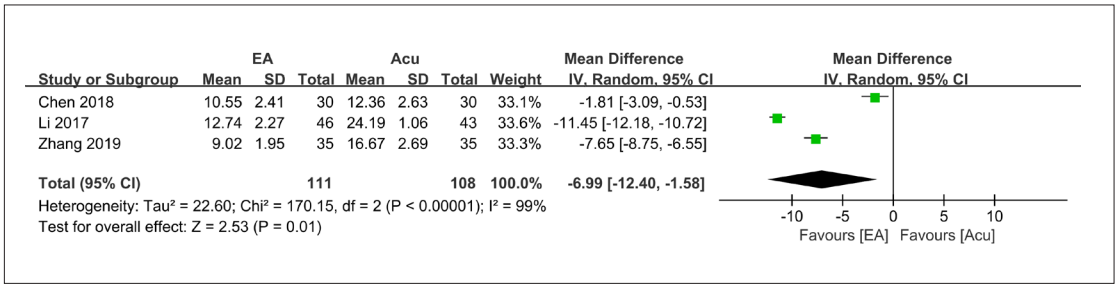

Fig. 6. Quality of Life: Electroacupuncture versus conventional acupuncture.

Quality of life

Meta-analysis was conducted by synthesizing 6 studies [14,15,17-20] using the SPHERE and the WHOQOL-BREF as output indicators that can represent the QoL. 3 studies [14,15,17] compared EA with conventional acupuncture, 2 studies [18,19] compared EA with sham EA, and 1 study [20] that compared EA with herbal medicine and herbal medicine alone were analyzed in small groups, and then the total results were analyzed again (Fig. 5).

The data were synthesized using the SMD to analyze the different indicators. The SPHERE is a parameter that is inversely proportional to the QoL standard, while the WHOQOL-BREF is a parameter that is proportional to the QoL level [21]. Therefore, negative modulus values were obtained.

For the same reason as above, a random-effects model was used. In the case of the EA versus acupuncture group, since 3 RCTs were studied with the same index, the result values were examined once again using the MD (Fig. 6).

In an analysis of EA and Acupuncture, the intervention group had a lower SPHERE index than the control group. When analyzed using the SMD, the heterogeneity of the 2 studies was high (I^2 = 98%), and the intervention group showed a statistically significant improvement in the QoL compared with the control group (SMD = −3.39, 95% CI: −6.38−−0.41, p = 0.03, I^2 = 98%).

Even when analyzed using the MD, the heterogeneity of the 2 studies was as high as I^2 = 99%, and the intervention group had significantly improved QoL compared with the control group. The effect size was larger than the SMD analysis (Fig. 6; MD = −6.99, 95% CI: −12.40− −1.58, p = 0.01, I^2 = 99%).

In the comparison of EA with sham EA, the SPHERE index was reduced more in the intervention group compared with the control group. The heterogeneity of the 2 studies was high (I^2 = 79%), and the degree of the SPHERE index reduction in the intervention group was not statistically significant (SMD = −1.30, 95% CI: −2.89-0.29, p = 0.11, I^2 = 79%).

In the comparison of EA with herbal medicine and herbal medicine alone, the WHOQOL-BREF index in the intervention group was determined to be significantly lower than the control group (SMD = −1.15, 95% CI: −1.70 − −0.60, p < 0.0001, I^2 = Not applicable).

When analyzing the three small groups, it appeared likely that EA could significantly improve the QoL compared with the control group. In the entire study, the heterogeneity was high (I^2 = 96%), but the heterogeneity between groups was low (I^2 = 5.4%).

In the quality evaluation using the GRADE tool, the quality of the meta-analysis was downgraded due to the RoB and indirect factors (Table 3).

Safety

1 study [20] reported ten cases of bleeding but no serious adverse events (AEs). 1 study [14] mentioned there were no AE due to treatment. There was no mention of AEs in the remaining 5 studies [15-19].

Reporting bias assessment

As the number of studies used for the meta-analysis in this study was less than 10, the publication bias was not evaluated, as advised by the Cochrane Handbook for Systematic Reviews of Interventions [12].

Discussion

CFS is the most severe form of chronic fatigue and a diagnosis is made if it meets 4 or more of the 8 major symptoms, including extreme exhibition lasting more than 24 hours after physical or mental occurrence, loss of memory or concentration, and unexposed muscle pain, and is characterized by no other organic lesions. It has been reported that the prevalence of CFS in Korea in patients who visited the Family Medicine Department is approximately 1.2% [22].

Treatment of unexplained chronic fatigue requires pinpointing the complex causes and approaching treatment in an integrated way. This is consistent with the theory of oriental medicine disease treatment. The Ministry of Health and Welfare, reported in 2020 that acupuncture is performed on 91% of patients in Korean clinical practice [23]. A survey in 2011, of Korean medicine doctors reported that 78.2% of doctors using acupuncture used EA [24].

Various case studies have reported that EA is empirically used in treating CFS patients with chronic fatigue, and 2 systematic reviews on acupuncture have been published recently [8,9]. However, no systematic review has been conducted on EA treatment for CFS.

Regarding the mechanism of EA, it has been reported that pain can be improved by EA by promoting the secretion of opioid

substances such as β-endorphin, enkephalin, and dynorphin through electrical stimulation [25]. In addition, animal experiments have shown that EA also helps the release of immune-related substances such as interleukins and tumor necrosis factor-alpha [26]. Despite the mechanisms of EA upon CFS having not been fully elucidated, it is thought that EA can be used as a treatment for the systemic effects of CFS. Therefore, this study was conducted to systematically examine RCTs of patients with CFS treated with EA to investigate the clinical effects of EA treatment.

In this review, 7 studies were analyzed, and in all RCTs, the intervention group showed statistically significant improvements in the level of fatigue and improvement in QoL compared with the control group. However, due to the large heterogeneity of the sample counts and the design of each study, meta-analysis was used to analyze the effect size of the statistics.

Examining the meta-analysis of the indicators of fatigue, the average value of the effect size was negative, even in the synthesis of small groups, and the comparison of the overall control group. Except for the results for EA vs. Acupuncture, EA showed statistical significance in reducing fatigue in all groups ($p < 0.01$). In each study, the level of heterogeneity was high. However, the heterogeneity between the results of the small groups was low.

In the QoL index, the average value of the effect size was also negative in the synthesis performed for the small groups, and in the comparison of the overall control group. Except for the EA vs. sham EA results, statistical significance was observed in all groups ($p < 0.01$). A large-scale study with a more robust design is needed to verify the effect of acupuncture.

As a result of analyzing the treatment used in the 7 included RCTs [14-20], ST36, BL23, CV4, and CV8, were frequently used. In the review by Zhang et al. ST36, BL18, BL23, GV20, and BL20 were frequently used acupoints [9]. Comparing these acupoints to a review conducted by Kim et al. [8], it was reported that ST36, BL23, BL18, GV20, BL15, BL20, CV4, CV6, CV17, SP6, BL12, HT7, and KI3 were the most frequently used across studies. This result was due to the large number of studies included in the review by Kim et al [8].

There have been studies in which the interventions varied depending on the patient's symptoms. For example, Li et al [16] used BL23 for insomnia and GB34 for muscle pain. Furthermore, Hu et al [20] suggested selection between; (1) CV 4, EX-HN 1 BL15, BL17, BL18, BL20; or (2) GV 4, CV 6, CV 4, ST 36, LI 4, LR3 depending on patient symptoms. CAM treatment tended to be used through pattern identification. When loose criteria were used, symptoms tended to appear because the condition was categorized as CFS. Only a small number of the acupoints were common between studies.

All studies [14-17,20] except EA vs. sham EA seemed to include one or more CV acupoints, which were considered to collectively regulate the function of human yin qi as the "sea of yin meridian" in Korean medicine [27]. In addition, because the CV acupoint is considered to be directly related to growth and reproductive function [28], it has been used empirically for various symptoms related to fatigue.

Most studies did not describe the types of needles in detail. Regarding the needle depth, 6 studies [14-16,18-20] reported the insertion of the needles until de qi, and 1 paper [17] reported an accurate depth of 15 mm. The frequency was also inconsistent between studies. 6 studies [15-20] described that the intensity of the current was adjusted according to the patient's tolerance level, 5 studies indicated that the treatment time was 30 minutes [14-17,20], and 2 studies indicated that the treatment time was 20 minutes [18,19]. There was a limitation in the reproduction process because the studies did not clearly state the number and type of needles, whether the torsion method was used, or the operator's background/training. Therefore, future randomized controlled clinical studies should detail these factors. However, since EA is a treatment applied in the clinical field, rather than unifying the intervention, the treatment should be described in detail according to the STRICTA guidelines so that it can be reproduced.

Regarding the RoB for evaluation, since the patients included in this study seemed to have a very high RoB, the quality evaluation performed using the GRADE tool was downgraded in all 7 studies. Regarding AEs, ten cases of bleeding were reported in 1 study [20], and no serious AEs were reported. However, because only 2 studies [14,20] reported AEs, confidence in the safety of the treatment could not be established. However, a study that examined AEs of acupuncture for other diseases, the side effects of EA treatment were reported in 41 of 555 cases, and no serious side effects were reported [29]. In the study of CFS, side effects should be reported more clearly in the future.

This study had several limitations. Firstly, all of the studies included were written in Chinese, limiting the generalizability of the results to other countries. Secondly, the RoB of the literature included in this study as evaluated by the Cochrane RoB tool was high, and the reliability of the research results was low. Therefore, attention should be paid to the analysis. Thirdly, the results of the study were generally positive, but other treatments could also have a similar effect on the symptoms of CFS and QoL. EA may have potential value as a therapy, but whether it provides specific treatment for CFS remains unclear. Fourthly, the effect size was determined by synthesizing studies with high heterogeneity due to the limited number of included studies. Statistically significant results were reported during the overall synthesis, but statistically insignificant results were also obtained when small groups with high homogeneity in the research design were compared. Finally, as the frequency, waveform, and acupoint used in each study were not unified, it was difficult to reach a consensus for EA.

A randomized controlled clinical study that addresses these limitations is required in the future. In particular, more studies are required that strictly follow the STRICTA guidelines. This will reduce the heterogeneity of studies on EA treatment.

Conclusion

A total of 7 RCTs were selected from 6 databases, and meta-analysis of EA treatment for patients with CFS was conducted. The EA group showed better clinical effects than the control group in terms of improved QoL and reduced fatigue. No serious AEs were reported during the intervention. However, further research is needed due to the high RoB in the reviewed studies; not all RCTs accurately reported the research method, all studies were conducted

in 1 country (China), and the number of included studies was small.

Author Contributions

Conceptualization: JWY. Methodology: JWY. Formal investigation: JWY, DHS and JWL. Data analysis: JWY and DHS. Writing original draft: JWY. Writing – review and editing: JWY, DHS, JHO and JWL.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Ethical Statement

Not applicable.

Data Availability

All relevant data are included in this manuscript.

References

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953–959.
[2] Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE et al. Chronic fatigue syndrome: A working case definition. Ann Intern Med 1988;108:387–389.
[3] Wessely S. The epidemiology of chronic fatigue syndrome. Epidemiol Rev 1995;17:139–151.
[4] Carolina XS, Andrew RL. Chronic fatigue syndrome: Progress and possibilities. Med J Aust 2020;212:428–433.
[5] Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N et al. Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: A systematic review for a National Institutes of Health pathways to prevention workshop. Ann Intern Med 2015;162:841–850.
[6] Terje A, Lee MS, Choi TY, Cao HJ, Liu JP. Complementary and alternative medicine for patients with chronic fatigue syndrome: A systematic review. BMC Complement Altern Med 2011;11:87.
[7] Wang JJ, Song YJ, Wu ZC, Chu XO, Wang XH, Wang XJ et al. A Meta-Analysis on Randomized Controlled Trials of Acupuncture Treatment of Chronic Fatigue Syndrome. Zhen Ci Yan Jiu 2009;34:421–428.
[8] Kim GK, Ryoo DW, Jeong SM, Kim SJ, Baek SW, Lee CH et al. A Systematic Review of Acupuncture for Chronic Fatigue Syndrome. Acupuncture 2017;34:93–112.
[9] Zhang Q, Gong J, Dong H, Xu S, Wang W, Huang G. Acupuncture for chronic fatigue syndrome: A systematic review and meta-analysis. Acupunct Med 2019;37:211–222.
[10] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8:336–341.
[11] MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A et al. Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): Extending the CONSORT statement. J Altern Complement Med 2010;22:167–180.
[12] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al [Internet]. Cochrane Handbook for Systematic Reviews of Interventions version 6.3. 2022 [cited 2022 Apr 7]. Available from: http://training.cochrane.org/handbook.
[13] Schünemann H, Brożek J, Guyatt G, Oxman A [Internet]. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group. 2013 [cited 2022 Apr 6]. Available from: http://guidelinedevelopment.org/handbook.
[14] Li J, Xie J, Pan Z, Guo X, Li Y, Fu R. Chronic fatigue syndrome treated with transcutaneous electrical acupoint stimulation: A randomized controlled trial. Zhongguo Zhen Jiu 2017;37:1276–1279. [in Chinese].
[15] Chen S [Dissertation]. Clinical comparative study on two different methods for chronic fatigue syndrome treatment. Guangzhou (China): Guangzhou University of Chinese Medicine; 2013. [in Chinese].
[16] Li W. Musical electro-acupuncture for the treatment of chronic fatigue syndrome 60 cases were clinically observed. Heilongjiang Med J 2014;27:405–406. [in Chinese].
[17] Zhang M, Song L, Wang B, Yang T. Clinical Study of Electro-Acupuncture Combined with Herbal Moxibustion at CV 8 in Treatment of CFS of Qi Deficiency. J Clin Acupunct Moxibustion 2019;35:19–22. [in Chinese].
[18] Zhu Y, Liang F, Cheng C, Wu X, Wang H, Bao K, et al. A Randomized Controlled Trial of Electroacupuncture for Chronic Fatigue Syndrome. Shanghai J Tradit Chin Med 2008;42:48–50. [in Chinese].
[19] Oh H [Dissertation]. Pathological rhythm characteristics of chronic fatigue syndrome and its adjustment mechanism of electroacupuncture. Chengdu (China): Chengdu University of Traditional Chinese Medicine;2006. [in Chinese].
[20] Hu Y [Dissertation]. Combination of electric acupuncture with xiaoyaowan to treat chronic fatigue syndrome. Guangzhou (China): Guangzhou University of Chinese Medicine; 2013. [in Chinese].
[21] Kang H. Statistical Considerations in Meta-Analysis. Hanyang Med Rev 2015;35:23–32. [in Korean].
[22] Kim CH, Shin HC, Won CW. Prevalence of chronic fatigue and chronic fatigue syndrome in Korea: Community-based primary care study. J Korean Med Sci 2005;20:529–534. [in Korean].
[23] Ministry of Health and Welfare [Internet]. Survey on the use of Korean medicine 2020. [cited 2022 Apr 13]. Available from: https://www.koms.or.kr/. [in Korean].
[24] Moon JS, Lee SH, Kim JE, Kim BY, Choi SM. A Survey on the Use of Electroacupuncture by Traditional Korean Medicine Doctor. J Korean Acupunct Moxibustion Soc 2011;28:53–68. [in Korean].
[25] Shin HK, Lee KH, Park DS. α2-Adrenoceptors are implicated in the electroacupuncture-induced analgesia of experimental chronic pain. J Korean Med 2004;25:67–77. [in Korean].
[26] Kim MR, Lee YM, Youn DH, Na CS. Effects of Laser and Electro Acupuncture Treatment with GB30 · GB34 on Change in Arthritis Rat. Korean J Acupunct 2019;36:189–199. [in Korean].
[27] Committee on Compilation of Textbook of Korean Society for Acupuncture & Moxibustion. Acupuncture & Moxibustion. Paju (Korea): Jipmoondang Publishing Company. 2008:2667–71, 137. [in Korean].
[28] Lee BH, Park JH, Kim HY, Kim SD, Yang HD, Lee HJ et al. A Review on the Absence of Accumulation Point in the Governer, Conception, Thoroughfare, Belt Vessel of Extra Meridian. Korean J Acupunct 2013;30:81–87. [in Korean].
[29] Kim DH, Kim KW, Kim JH, Kim HH, Park JM, Yoo JH et al. Prospective Observational Study of Acupuncture Adverse Events: 50 Patients Hospitalized for Peripheral Facial Palsy Treatments. J Korean Acupunct Moxibustion Soc 2011;28:65–76. [in Korean].