ORIGINAL RESEARCH

Acupuncture for Chronic Fatigue Syndrome: A Randomized, Sham-controlled Trial With Single-blinded Design

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ABSTRACT

Context • Given that the etiology of chronic fatigue syndrome (CFS) is believed to be multidimensional, interventions generally have been nonspecific and typically produce only mild to moderate effects. In medical practice, treatment for CFS remains largely symptomatic. Preliminary evidence of the efficacy of acupuncture for CFS is available, but the field has lacked high-quality trials.

Objective • The research team conducted the study to determine the efficacy of acupuncture for CFS.

Design • A two-arm, randomized, controlled, single-blinded design was adopted.

Setting • The study took place in a teaching laboratory at the School of Chinese Medicine at the University of Hong Kong, Hong Kong, China.

Participants • Recruited through press publicity in Hong Kong, 127 individuals—40 men and 87 women—participated in the study.

Intervention • Through careful implementation of sham acupuncture in the control group (CG), the study blinded all participants with regard to their experimental or control status. The treatment regime was 2 sessions/wk for 4 consecutive wk.

Outcome Measures • Measures of fatigue (Chalder's Fatigue Scale), health-related quality of life (SF-12), and general mental health (GHQ-12) were taken at baseline and upon completion of treatment.

Results • Ninety-nine participants completed the interventions, with 50 and 49 participants in the experimental group (EG) and CG respectively. Repeated measures ANOVA revealed a significant decrease in physical ($F_{1,93}$ = 4.327; P = .040) and mental fatigue ($F_{1,96}$ = 10.451; P = .002) and improvement in the physical component score of SF-12 ($F_{1,93}$ = 4.774; P = .031). Considerable effects with Cohen's d were observed in the sham-control group: 0.92, 0.78, and 0.38 for the three scores, respectively. These positive effects could have included some therapeutic effects due to pressure on the acupuncture points from the sham needles in addition to normal placebo effects. The EG showed moderate net effect sizes with Cohen's d: 0.52, 0.63, and 0.54 for the three outcome measures, respectively.

Conclusion • Despite considerable positive effects for the CG, the EG demonstrated significant net-effect sizes at a moderate magnitude in physical and mental fatigue and in the physical component of health-related quality of life. The impacts on general mental health outcomes appeared to be smaller. (*Altern Ther Health Med.* 2013;19(4):21-26.)

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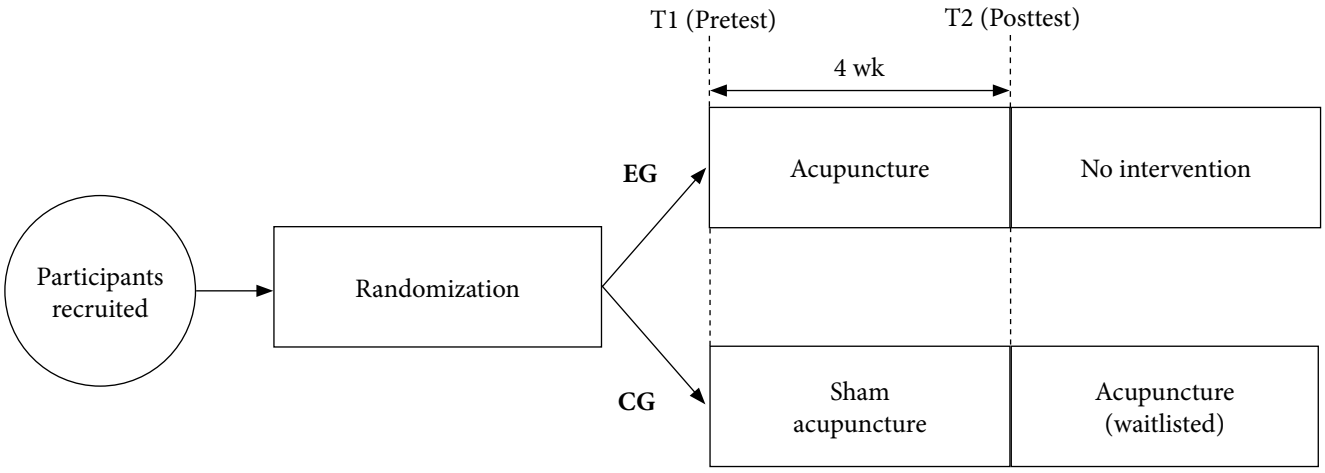
In light of emerging evidence, chronic fatigue syndrome (CFS) was adopted as a disease entity by the US Center for Disease Control and Prevention (CDC) in the 1980s.[1] CFS is conceptualized as a functional disorder characterized by persistent fatigue (6 mo or longer) that cannot be explained by other medical conditions. Although the diagnosis of CFS remains largely symptom-based, a positive diagnostic approach has been established as research on the disease has advanced. Estimates for the prevalence of CFS range between 0.7% and 2.8% in the general adult population.[2] Variations in the operational definition of CFS accounted for much of the discrepancy across studies.

Figure 1. Procedures for the Randomized, Controlled Trial



Abbreviations: EG = experimental group; CG = control group.

The etiology of CFS is believed to be multidimensional. The prevailing theories explaining CFS include neuroendocrine dysfunction,[3] viral infection,[4] immunological abnormalities,[5] genetic predisposition,[6] psychosomatic responses,[7] and mental disorders.[8] Regarding treatments, researchers have evaluated the efficacy of pharmacological interventions,[9] physical exercise,[10] cognitive behavioral therapy,[11] and immunological and antiviral treatments.[12] Probably due to the multidimensional nature of the etiology, interventions for CFS are nonspecific and typically produce mild to moderate effects only. In medical practice, treatment for CFS remains largely symptomatic. Acupuncture for CFS has been evaluated in a number of clinical trials, suggesting preliminary evidence of efficacy.[13] A common inadequacy of previous studies is the lack of a well-designed control group (CG) so that participants are blinded with regard to whether they are receiving the treatment or not. With advances in research methods, the techniques of using sham acupuncture in randomized, controlled trials have been steadily refined since the 1990s.[14] Using well-designed sham acupuncture and carefully planned procedures, single blinding can be achieved; that is, participants are blinded to their experimental or control status. Participants in both the experimental group (EG) and the CG appear to go through the same procedures and feel that they have received standard acupuncture intervention. This method has been employed in clinical trials of acupuncture for various conditions, such as knee osteoarthritis,[15] low-back pain,[16] and nausea and vomiting in early pregnancy.[17]

In light of the advances in research methods and the shortcomings of previous clinical trials, the current study aimed to conduct a randomized, sham-controlled trial of acupuncture for treatment of CFS. The research team aimed to achieve single blinding through carefully planned procedures for both the EG and CG.

METHODS

The present study was conducted as a single-blinded, randomized, controlled clinical trial with a 2 × 2, mixed factorial design.

Participants

Participants were recruited through press publicity in Hong Kong. In the week following the publicity, a total of 605 people called and indicated interest in joining the study. Preliminary screening of potential participants was performed over the phone. Inclusion criteria were (1) being aged between 18 and 50, (2) not having current medical conditions associated with chronic fatigue, (3) having no history of substance or alcohol abuse, and (4) meeting the CDC's diagnostic criteria for CFS.[18] There were 137 participants who met the inclusion criteria. Eligible participants were further interviewed at the research office to provide written informed consent for participation in the study and to complete the baseline measurements.

Randomization

Assuming a moderate effect size of 0.6, 44 participants were required for each arm of this two-arm, randomized, controlled trial to meet a .05 significance level (2-tailed) and a power of 0.8.[19] To allow a buffer for possible dropouts and missing data, the study aimed to recruit at least 60 participants for each group.

Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence. This procedure minimized the potential systematic differences between participants who were enrolled in the trial sequentially.

Of the 137 voluntary participants who were randomly assigned either to the EG (n = 68) or to the concurrent CG (n = 69), 127 accepted the allocation and participated in the

Table 1. The Locations and Functions of the Acupuncture Points Selected

Acupuncture Point	Chinese Pinyin	Location	Key Functions
Du mai 20 (DU20)	*Bai hui*	The midpoint of the line connecting the apexes of the two auricles, located at the midline of the head	Restores the overall *qi* balance of the body; harmonizes psychic functions
Stomach 36 (ST36, bilateral)	*Zu san li*	3 cm below ST35, one finger width lateral from the anterior border of the tibia	Tonifies qi and blood; relieves abdominal discomforts and digestive/elimination dysfunctions
Spleen 6 (SP6, bilateral)	*San yin jiao*	3 cm directly above the tip of the medial malleolus on the posterior border of the tibia	Tonifies yin and blood; enhances sexual functions; relieves menstrual dysfunctions (for women); relieves insomnia and anxiety symptoms

study (62 in the EG; 65 in the CG).

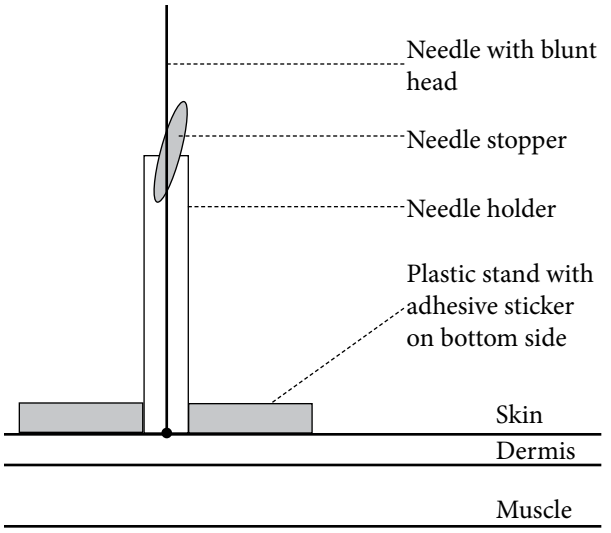
The study's procedures are illustrated in Figure 1. Upon completion of the study, group allocations were revealed to participants in both groups. For ethical reason, participants in the CG were offered true acupuncture treatment at the end of the study.

Intervention

The intervention was delivered in a teaching laboratory at the School of Chinese Medicine at the University of Hong Kong in Hong Kong, China. For the EG, the acupuncture treatment comprised a total of eight 30-minute sessions over a period of 4 consecutive weeks. An individual room was prepared for each participant to undergo the intervention. The acupuncture points were chosen in accordance with the theories of traditional Chinese medicine (TCM). Table 1 summarizes the anatomical location and key functions of the five selected acupuncture points, which were DU20, ST36 (bilateral), and SP6 (bilateral). Five needles were used for each acupuncture session. All interventions were delivered by a registered TCM practitioner with over 10 years of clinical experience in acupuncture.

In the CG, sham acupuncture was administered for each participant following exactly the same treatment schedule as the EG. All the interventions were delivered by the same TCM practitioner who delivered treatment to the EG. Before the actual clinical trial, this practitioner received special training in the administration of sham acupuncture, delivered in such a way that the participants were blinded and believed that they had received standard acupuncture. To perform sham acupuncture, specially-designed needles were used.[14] Figure 2 illustrates the design of the sham acupuncture used in the study. The tips of the needles were blunt. These needles were held in place by a specially-designed needle holder and plastic stand so that the needle provided only a pricking sensation on the skin, without penetrating it. For the EG, the appearance of the real acupuncture was exactly the same as the sham acupuncture. However, the needles were longer, and the tips were sharp. With the matching plastic stand, the needle could penetrate the skin to the desired depth.

Figure 2. Sham Acupuncture Used in the Study



The same acupuncture points were used for the CG as for the EG. Although the nonpenetration stimulation of these points could lead to some therapeutic effects, these points were preferred to nonacupuncture points to maintain the blinding effects. Since participants might communicate with each other about their experiences in receiving the intervention, it was important to ensure that the interventions in both groups looked the same to participants. The research team's experience suggested that using the same set of points was essential for blinding the participants.

Each intervention session lasted about 30 minutes, and the session flow was exactly the same in both the EG and CG. Each participant received the intervention in an individual room and lay on a bed throughout the process. Five needles inside needle stands were administered to the five selected acupuncture points.

For the EG, needle manipulation (twilling and moving

the needle up and down rapidly) for enhancing the acupuncture sensation (called *de qi* in Chinese medicine), was performed at the beginning, middle, and end of every intervention session. Each round of needle manipulation on the five needles took about 3 minutes to complete.

Measures

Each participant was instructed to complete a set of questionnaires prior to and immediately after the intervention. The data collection was administered by a research assistant who knew the group allocations of the participants but was not involved in delivering the intervention. The structured questionnaires included the following measures:

Chalder's Fatigue Scale. This scale was the primary outcome measure in the study.[20] It is a 14-item, self-report scale producing two subscores, namely the physical and mental fatigue scores. A higher score indicates more severe symptoms.

General Health Questionnaire 12 (GHQ-12). This questionnaire is a 12-item, self-report scale measuring general mental health status.[21,22] A higher score indicates more severe symptoms for common mental disorders.

Short Form 12 (SF-12).[23] This form assesses health-related quality of life. It is a 12-item, self-report scale producing two subscores, namely the physical and mental component scores. A higher score indicates a better health-related quality of life.

Statistical analysis

Repeated measures ANOVA (2×2 design) was performed to compare the pre/post changes in fatigue scores for the EG and CG. Cohen's *d* was computed for both groups to evaluate the effect size of the intervention. Net effect size was computed by subtracting Cohen's *d* of the CG from Cohen's *d* of the EG. The statistical analyses were repeated for the secondary outcome measures, which were the GHQ and the physical- and mental-component scores of the SF-12.

RESULTS

The analysis included participants who completed six or more intervention sessions, resulting in an effective sample size of 99, with 50 and 49 in the EG and CG, respectively. The overall completion rate was 80.0%.

The demographic characteristics of the study's sample are summarized in Table 2. Among the 99 participants, 31 were men, and 68 were women. The mean age for all participants was 40.9 years (SD = 6.5). The majority of the participants (69.7%) were working full-time. No significant differences in demographic characteristics existed between participants in the EG and the CG.

A series of mixed group factorial ANOVAs was performed between the EG and CG to examine the net effect of acupuncture for CFS. The repeated measures ANOVA revealed a significant decrease in physical ($F_{1,93}$ = 4.327; P = .040) and mental fatigue ($F_{1,96}$ = 10.451; P = .002) and improvement in the physical component score of SF-12 ($F_{1,93}$ = 4.774; P = .031). See Table 3.

Table 2. Demographic Characteristics of Participants

	EG[a] (n = 50)	CG[a] (n = 49)
Age, y, Mean (SD)	39.8 (6.6)	42.0 (6.5)
Gender, n (%)		
Male	14 (28.0)	17 (34.7)
Female	36 (72.0)	32 (65.3)
Previous Acupuncture Experience, n (%)		
Yes	25 (50.0)	25 (51.0)
No	25 (50.0)	24 (49.0)
Educational Level Achieved, n (%)		
Primary	4 (8.0)	5 (10.2)
Secondary	23 (46.0)	27 (55.1)
Tertiary	23 (46.0)	17 (34.7)
Employment, n (%)		
Full-time	37 (74.0)	32 (65.3)
Part-time	3 (6.0)	6 (12.3)
Unemployed	10 (20.0)	11 (22.4)

Abbreviations: EG = experimental group; CG = control group.
[a]No significant difference exists between the two groups for all demographic variables.

The main effect was assessed in all of the measures' variables, indicating that individuals from both the EG and the CG showed significant improvement across the time of assessment. Of those variables, significant interactions were found for the physical-fatigue score, the mental-fatigue score, and the physical component score of SF-12.

To evaluate the effect sizes of the interventions, Cohen's *d* for each outcome variable was computed. The results are summarized in Table 4. According to the interpretation of the resultant effect sizes suggested by Cohen, both the EG and the CG had large positive effects.[24] For the EG, the effect size for various outcome measures ranged between 0.92 and 1.44, whereas for the CG, the effect size ranged between 0.38 and 1.16. Net effect sizes for the intervention were computed by subtracting the placebo effect from the intervention effect. Three of the variables—namely physical fatigue, mental fatigue, and the physical component score of SF-12—demonstrated moderate net effect sizes with Cohen's *d*: 0.52, 0.63, and .054 for the three scores, respectively.

Table 3. Repeated-measures ANOVA

	EG (n = 50)				CG (n = 49)				Repeated-measures ANOVA			
	T0		T1		T0		T1		Variable (Main Effect)		Variable Group (Interaction Effect)	
Measures	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F Score**	***P* Value**	**F Score**	***P* Value**
Chalder's Fatigue Scale												
Physical	30.67	5.257	22.29	6.439	29.17	5.397	23.70	6.528	98.271	.0[c]	4.327	.040[a]
Mental	20.65	5.122	13.65	4.880	18.55	5.042	14.82	4.558	112.95	.0[c]	10.451	.002[b]
GHQ-12												
	4.98	4.265	1.43	2.828	4.88	3.751	1.06	2.828	70.747	.0[c]	0.089	.766
SF-12												
Physical	34.43	7.676	41.36	7.574	34.99	9.369	38.72	10.579	53.132	.0[c]	4.774	.031[a]
Mental	38.89	9.665	47.96	9.419	40.52	10.122	47.76	10.693	44.028	.0[c]	0.569	.452

Abbreviations: EG = experimental group; CG = control group; GHQ-12 = general health questionnaire 12; SF-12 = short form 12.

[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$

Table 4. Effect Sizes of Interventions

	Effect Size[a]		
Measures	**EG**	**CG**	**Net Effect Size[b]**
Chalder's Fatigue Scale			
Physical	1.44	0.92	**0.52**
Mental	1.41	0.78	**0.63**
GHQ-12			
	0.99	1.16	0.17
SF-12			
Physical	0.92	0.38	**0.54**
Mental	0.96	0.70	0.26

Abbreviations: EG = experimental group; CG = control group; GHQ-12 = general health questionnaire 12; SF-12 = short form 12.

[a]Effect sizes measured with Cohen's *d*.
[b]Net effect sizes above 0.4 in bold.

DISCUSSION

The current study addressed a key limitation of the previous trials of acupuncture for CFS (ie, the lack of a proper CG in which the control techniques approximate acupuncture treatments). By using well-designed sham acupuncture and paying careful attention to the logistics of treatment delivery, single blinding was achieved in a clinical trial in which participants in both the EG and CG had apparently the same experience in the course of treatment. This advancement in study design elevated the level of evidence for the efficacy of acupuncture for CFS.

As anticipated, considerable positive effects, both normal placebo effects and some possible therapeutic effects from pressure on acupuncture points, were observed in the current study's CG. That group's effect sizes (Cohen's *d*) for physical and mental fatigue and the physical component score of SF-12 were 0.92, 0.78, and 0.38, respectively. These findings supported the necessity of having a proper CG for acupuncture trials.

Despite the considerable positive effects in the CG, acupuncture demonstrated significant efficacy for the EG. Moderate in magnitude, the net effect sizes with Cohen's *d* for physical fatigue, mental fatigue, and the physical component score of SF-12 measured 0.52, 0.63, and 0.54 for the three outcome measures, respectively.

A review of previous clinical trials of acupuncture suggests that sham acupuncture tends to be efficacious to some extent.[25] Therefore, the results revealed in the current study are probably rather conservative estimates of the actual net effect size of acupuncture for CFS.

At 80%, the overall treatment completion rate seems satisfactory for an eight-session treatment. Participants needed to come to the research center during office hours twice per week for 4 consecutive weeks.

No adverse events occurred throughout the study. These results suggest a satisfactory acceptability of acupuncture as a treatment option for CFS patients.

This study had a number of limitations. First, the sham acupuncture was administered at exactly the same set of acupuncture points as that of the EG. The blunt sham needle might have produced a certain degree of acupressure effect, and thus, some therapeutic effects in addition to normal placebo effects might have been part of the observed positive effects for the CG. The net effect sizes revealed in the study are probably rather conservative estimates of the efficacy of acupuncture for CFS. Second, the clinical trial was conducted in the research facilities of a university. That location might have had some psychological impacts on the participants, and perhaps, inflated the responses to treatment. It is recommended that further clinical trials be conducted in a nonuniversity environment. Third, geographical effects on the clinical trial might have occurred. Located in a coastal, tropical region, Hong Kong has a long summer that is hot and humid. According to the systemic theories of traditional Chinese medicine, a strong connection exists between human beings and their environment. Also, the efficacy of the chosen set of acupuncture points needs to be further evaluated in other geographical locations.

CONCLUSION

The current study successfully adopted a method of sham acupuncture and achieved single blinding in the implementation of a randomized, controlled trial of acupuncture for CFS. Findings revealed moderate net effect sizes on some outcome variables: physical and mental fatigue and the physical component score of SF-12. Since sham acupuncture may also be efficacious to some extent, the observed net effect sizes are probably conservative estimates of the efficacy of acupuncture. In light of the favorable results, repetition of the trial in nonuniversity and nontropical locations are recommended.

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