Dose-Effect of Long-Snake-Like Moxibustion for Chronic Fatigue Syndrome: Study Protocol for a Randomized Controlled Trial

Tingting Ma (matingting@cdutcm.edu.cn)
Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Rui Gong
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Rui Zheng
Chengdu University of Traditional Chinese Medicine Wenjiang Campus: Chengdu University of Traditional Chinese Medicine
Jie Wu
Chengdu University of Traditional Chinese Medicine Affiliated Hospital

Study protocol

Keywords: Chronic fatigue syndrome (CFS), long-snake-like moxibustion, dose-effect relationship, randomized controlled trial, study protocol

DOI: https://doi.org/10.21203/rs.3.rs-267403/v1

Abstract

Background

Chronic fatigue syndrome (CFS) is a disease with high incidence rate and great impact on life, but it lacks for specific pharmacological treatment and diagnostic indicators. In the theory of traditional Chinese medicine (TCM), fatigue is the result of Yang deficiency. Long-snake-like moxibustion, as one of a special moxa therapy, has been applied in Yang deficiency patients for thousands of years in China and it is used widely to relieve fatigue symptoms for its strong function of Yang warming. However, the does-effect relationship is unclear in the moxibustion research. Hence, we design this trial to assess the duration-effect of long-snake-like moxibustion through combining measurements of the subjective patient-reported scales with objective medical infrared imaging technology—Thermal Texture Maps (TTM).

Methods

This is a single-center, randomized controlled trial. Thirty healthy women and sixty female CFS patients will be recruited to receive the first TTM scanning, then CFS patients will be allocated to 60-minute long-snake-like moxibustion (Group A) and 30-minute long-snake-like moxibustion (Group B) equally. These two groups will receive corresponding treatment once a day, three sessions per week every other day for consecutive 4 weeks. The second TTM scanning will be employed for CFS patients after the end of treatment. The primary outcome will be the score improvement of the Fatigue scale-14 (FS-14). Secondary outcomes include the change of the Self-rating depression scale (SDS),the Self-rating anxiety scale (SAS), and the Symptoms Scale of spleen-kidney Yang deficiency.

Discussion

The trial will provide evidence for the choice of treatment duration for long-snake-like moxibustion in treating CFS. The results will contribute to explore the dose-effect relationship of moxibustion, and optimize the efficacy of moxibustion therapy.

Trial registration:

Chinese Clinical Trail Registry (No. ChiCTR2000041000), on 16th December, 2020, http://www.chictr.org.cn/showproj.aspx?proj=62488

Background

Chronic fatigue syndrome (CFS) is characterized as the presence of persistent, debilitating fatigue lasting for a minimum of six months and being not relieved by rest[1]. The fatigue and its accompanied symptoms, such as sleep disturbance, pain, sore throat, or impaired short-term memory or concentration,

greatly affect patients' work and life quality. Among the 40% global prevalence of CFS, most of suffers are women[2]. The medical cause for CFS is still not clear, so no specific pharmacological treatment is recommended. Acupuncture[3], yoga[4], cognitive behavioral therapy (CBT) or graded exercise therapy (GET)[5–7] are promising approaches to the treatment.

In the theory of traditional Chinese Medicine (TCM), fatigue is the result of Yang deficiency, and moxibustion can produce yang-warming effect to improve the deficient yang for zang and fu. Although the mechanism of CFS treated by moxibustion is not fully explained, the moxibustion therapy is effective in relief of symptoms[8, 9]. Long-snake-like moxibustion is also called as Du moxibustion. In this special moxa therapy, a large range of moxa cones or sticks over herbs or ginger are applied on the Governor Vessel from GV14 to GV2 to generate a strong warming stimulation. In our previous study[10], we improved the long-snake-like moxibustion technique through applying moxa box over ginger slices on the back from GV14 to GV2 as well as the same level of the first lateral line of bladder meridian to increase clinical operability and enhance therapeutic effect.

A variety of factors influence the therapeutic efficacy of moxibustion, especially moxibustion dose, which includes moxibustion duration, moxibustion frequency, moxibustion amount-size and number of moxa cone[11–14]. None studies have focused on the dose-effect of moxibustion for CFS up to now, therefore, we designed this trail to investigate the relationship of long-snake-like moxibustion duration and effect in the treatment of CFS by combining subjective scales and objective measurement for assessment.

So far, CFS trials into the efficacy and safety of therapies have employed the self-reported subjective measurements as the outcome assessments for evaluating subjective physical function, anxiety, depression, and pain improvement, such as the Chalder Fatigue Scale, Short Form 36 Health Survey Questionnaire (SF-36), Anxiety and Depression Scale and visual analogue pain rating scale[15]. In addition, biological markers and imaging techniques such as MRI are also used to aid clinical diagnoses and effect assessments[16, 17]. In this trial, we try to use the Thermal Texture Maps (TTM)—a thermography technique of evaluating thermal signatures of the body through holistic interpretation of infrared images to aid CFS diagnosis and moxibustion dose-effect assessment.

Methods And Design

Design

A single-center, randomized, controlled trial will be conducted at the Center of Preventive Medicine of Hospital of Chengdu University of TCM. 30 healthy women (Group C) without moxibustion therapy and 60 CFS female patients with a treatment period of 4 weeks (3 sessions per week, every other day) will be recruited. When meeting the inclusion criteria, 60 CFS patients will be randomly allocated to group of 60-minute long-snake-like moxibustion (Group A), or 30-minute long-snake-like moxibustion (Group B) in a 1:1 ratio after exclusion. The study flow is depicted in Figure 1.

Randomization and allocation concealment

Eligible CFS participants will be randomly allocated to treatment in Group A or Group B. Random numbers will be generated by Statistics Analysis System (SAS), and then placed folded over in opaque envelopes. A research assistant, who is uninvolved with assessment or treatment, is responsible for keeping the original random allocation sequences, printing serial numbers on the outside of the envelopes, and sealing the envelopes. All envelopes will be put into a plastic container in numerical order. Once the patients are assessed to meet the inclusion criteria and informed consent forms, the investigators will open the envelopes in turn. Investigators who assess outcomes and analyze results are masked to treatment allocation.

Blinding

The outcome assessors and statistical analysts will be blinded to the intervention assignments throughout the trial.

Ethics and clinical registration

This trial will follow the rules of the Declaration of Helsinki and the Good Clinical Practice Guidelines, with unique registration number (ChiCTR2000041000) at http://www.chictr.org.cn. The protocol has been approved by the Ethics Committee of Hospital of Chengdu University of TCM in 2020 (NO.2020KL-046). Written informed consent will be obtained from every patient before participation.

Participates

Healthy females aged 18 to 60 will be recruited as healthy participates. Patients will be recruited if : (1) females aged 18 to 60; (2) chronic fatigue is lasting and can’t be explained by illness; (3) debilitating fatigue predates and is accompanied by at least 4 of 8 designated symptoms: post-exertional malaise lasting more than 24 hours; unrefreshing sleep; impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; headaches of a new type, pattern, or severity; muscle pain; multi-joint pain without swelling or redness; sore throat; and tender cervical/axillary lymph nodes. Accompanying symptoms must have persisted or recurred during 6 or more consecutive months of illness.

Patients should also meet the inclusion criteria of the pattern of spleen and kidney Yang deficiency: (1) 3 of 5 main symptoms: being afraid of cold, limb and/or lower back coldness; fatigue; breath shortness; poor appetite; and weakness of lower back and knee. (2) 2 of 6 accompanied symptoms: cold pain of lower back; stomach and/or abdominal fullness; loose stool; frequent night urination; teeth-mark tongue; and deep and weak pulse.

Exclusion criteria are presence of: (1) pregnancy or lactation; (2) diseases definitely influencing TTM results, such as scoliosis, limb deformity, etc.; (3) poor understanding or expression; (4) obviously damaged and scarred skin or ginger-sensibility.

Parts of participants will be recruited from the hospital. The other ways of participant recruitment are electronic posters on WeChat or posters displayed in hospitals and communities. A face-to-face interview will be held by the clinical trial coordinator to ensure all meet the inclusion criteria.

Intervention

Practitioners

Certified acupuncturists with TCM license and more than 2-year experience in clinics will be trained to participate in this trial. The training includes the correct manipulation of long-snake-like moxibustion.

Group A: 60-minute long-snake-like moxibustion

Patients in prone position with the whole back exposure will receive the ginger-indirect moxibustion on Governor Vessel and Bladder Meridian. Ginger slices for 2mm in thickness will be placed on the back from GV14 to GV2 to cover the area of the Governor Vessel and the first lateral line of Bladder Meridian (fig 2), then five or six three-hole Moxa boxes (the number of boxes depends on the patients' height; fig 3) will be put on them. The distance between the center of nearby holes is 4.8cm to ensure the temperature of moxa sticks (pure-mugwort moxa stick; 20 cm in length and 18 mm in diameter; Hwato, Suzhou, China, PRC) cover the Governor Vessel and the first lateral line of Bladder Meridian. During the 60-minute ginger-indirect moxibustion treatment, the depth of moxa sticks will be regulated every five minutes to maintain full combustion and obtain equal warm stimulation.

Patients will receive 12 sessions of moxibustion treatment over a period of 4 weeks (1 session per day, 3 sessions per week, every other day).

Group B: 30-minute long-snake-like moxibustion

The treatment process is as the same as in Group A, with a moxibustion duration of 30 minutes.

Outcome measures

Primary

In this trial, the score improvement based on the Fatigue scale-14 (FS-14) will be used as the primary outcome measurement. As a standardized questionnaire to reflect physical fatigue and mental figure, FS-14 comprises 14 questions, each of which has two options (yes or no) with a score of 0–1 (0=no, 1=yes),

with a total score ranging from 0 to 14[18, 19]. Higher scores indicate a higher level of chronic fatigue. It will be assessed at baseline and week 4 (the end of treatment).

Secondary

The secondary outcomes include the change of the Self-rating depression scale (SDS)、the Self-rating anxiety scale (SAS), and the Symptoms Scale of spleen-kidney Yang deficiency.

The Symptoms Scale of spleen-kidney Yang deficiency is a four-rate scale designed to evaluate the symptoms based on the TCM syndrome differentiation (table 1). It consists of primary symptoms with a ranging score of 0-6 of cold limbs, fatigue, breath shortness, poor appetite, weakness of lower back or knees, and secondary symptoms with a ranging score of 0-3 of lower back cold pain, stomach or abdomen fullness, loose stool, frequent night urination. Higher scores indicate a higher level of spleen-kidney Yang deficiency.

All secondary outcomes will be assessed at baseline and week 4 (the end of treatment).

Thermal Texture Maps (TTM) scanning process

90 eligible subjects (30 CFS female patients in Group A, 30 CFS female patients in Group B, and 30 healthy women in Group C) will receive TTM (Digital Medical Infrared Imaging System, MTI-ex pro-2013, Chongqing, China) scanning after inclusion, and only patients in Group A and B will receive the 2nd TTM scanning after 4-week treatment. To weaken the influence of external thermo-source from moxibustion in the images, the 2nd TTM scanning will be employed 5 days after the end of treatment. On the thermal map, the temperature value or thermal signatures (irregularity, asymmetry, discontinuity) will be recorded in the typical area, meridians or acupoints, including the back, spine, chest, abdomen, four limbs, head, the governor vessel from GV14 to GV2, the conception vessel from CV22 to CV2, and GV14, CV17, CV8. Comparison between healthy subjects and CFS patients, self-comparison before and after treatment will be made.

To minimize the impact of outside temperature, all the scanning will be conducted at the health examination center of hospital of Chengdu university of TCM in the morning, with a controlled room temperature of 24℃±2℃ and humidity of 20%±10%, without obvious air flow, strong light and infrared radiation source.

The process is as below：

1. Fill the personal health information form before scanning, which contains the medical history and the state of body condition in all organs;
2. Remove the ornaments, loosen the bra, and relax hair in advance. Have a rest of 30 minutes at rest room before scanning;
3. In prior to the scanning, patients will be asked to take all clothing off and expose the body in a temperature-controlled room for 10-15 minutes. Then images will be taken in front vs. back, left vs.

right to assess overall topological features of the whole body.

The notices are as below：

1. Fast for at least 2 hours prior to the scanning;
2. Before the scanning, alcohol should be stopped for at least 24 hours, the use of medications as vasodilator or vasoconstrictors are stopped for at least 4 hours, vigorous exercise is forbidden for at least 4 hours, other stimulants are stopped for at least 2 hours and hand washing is stopped for at least 30 minutes;
3. Skin conditioning such as use of cosmetics and perfume should be minimized, and a dress of looser clothing is advised;
4. No scanning during menstruation.

Sample size

Based on our preliminary study[20], in which an improvement of 2.45 on the FS-14 score after 60-minutes Long-snake moxibustion therapy was detected, we expect a difference of 0.4 in the mean improvement of FS-14 score. With a desired power of 0.9 and a significance of 0.05, the number of required patients is 27 per group. Taking into consideration a dropout rate of 10%, we plan to include a total number of patients of 90.

Statistical methods

All of the data analysis will be based on an intention-to-treat population, replacing missing data by the last-observation-carried-forward method. Quantitative data will be shown by mean with standard deviation (SD) or median with percentile (QL-QU), while qualitative variables will be expressed by frequency and proportion. The change of outcome will be shown by mean and 95% certificate interval (CI), by setting the absolute value at baseline as starting point. All the statistical analyses will be performed with R software version 3.6.3 (R Development Core Team, Vienna, Austrian). A two-sided test will be applied for all available data, and a P value <0.05 is considered statistically significant.

Data collection and quality control

The original data will be recorded in paper case report form (CRF) and then filled in a spreadsheet. An independent investigator will check the original data to ensure the consistency of CRF and spreadsheet. Only the principal investigators and clinical investigators are qualified to review the data. Before the start of trial, all involved researchers will undergo training to guarantee the full understanding of study protocol, research process and CRF-filling. Additionally, once the eligible participants are enrolled, full communication about possible benefits and risks will be made and comfortable treatment environment will be provided to ensure participants' compliance. For participants with poor compliance, investigators should contact them by phone to acquire the outcome data, possible reasons and encourage them to complete the study.

Discussion

Due to the non-organic pathophysiology, CFS is associated with suboptimal health status[21] and the present treatment of CFS is given based on limited or even contradictory evidence from clinical studies[22-24]. CFS is named fatigue syndrome in TCM theory and Yang-qi deficiency is regarded as the main reason. Yang qi is thought to be the vital motivity, so organs will become hypofunctional once Yang qi decreases. Moxa therapy has been applied in Yang deficiency patients for thousands of years in China and it is used widely to relieve fatigue symptoms[25].

The dose-effect relationship is the key issue in the moxibustion research. Key factors that determine the moxibustion dose include the treatment duration, frequency, the moxa extent and amount of moxa cones/sticks. However, the relationship between the dose of moxa stimulation and the resulting therapeutic efficacy has not yet been established, and previous studies have shown that the above dose factors affect efficacy to a different degree in different diseases. In the study of moxibustion in treating diarrhea-predominant irritable bowel syndrome, aconite cake-separated moxibustion with treatment regimen of 3 treatments/wk. and 1 cone/treatment appeared to produce better therapeutic effects compared with the regimen of 6 treatments/wk. and 2 cone/treatment[14]. Another study on suspended moxibustion for focal cerebral ischemia/reperfusion injury indicated a greater anti-apoptotic effect of 35-minute moxibustion than 15-minute moxibustion[13]. When treating depression-like behavior disorder in rats, prolonged duration of moxibustion under the optimal extent could increase the level of 5-HT[12]. In the treatment of chronic neck pain with the direct moxibustion of small moxa cone, a trend of effect improvement was related to an increase of the amount of moxa cones, when the other dose factors were constant[11]. The duration of long-snake-like moxibustion is a key factor in optimizing efficacy, but the treatment duration in treating CFS varies[26, 27]. In this trial, the duration-effect relationship will be studied for long-snake-like moxibustion employed from GV14 to GV2 as well as the same level of bladder meridian's first lateral line on the back. The result will provide evidence of treatment duration choice for long snake-like moxibustion in treating CFS, and enrich the content of dose-effect research of moxibustion therapy.

As for the lack of diagnostic indicators, the diagnosis and therapeutic measurement of CFS lie on the application of patient-reported outcome scales[28, 29], such as FSS (Fatigue Severity Scale), SPHERE, Chalder Fatigue Questionnaire, VAS (Visual Analogue Pain Scale), SDS, SAS, et al. Such tools focus on the improvement of functional abilities and emotional well-being, which reflect clinical features of CFS. Researches on the biomarkers of CFS have revealed that the disorder in neuro-immuno-endocrinological pattern is part of the pathophysiological mechanisms[30, 31], and functional (non-structural) changes in the brain are found by structural and functional MRI[17], but all of them can't fully reveal a CFS-specific measure. The research efforts are still made to seek biomarkers or new technology to aid aetiological understanding and treatment options for CFS.

A large body of evidence has showed that diseases or deviation from normal functioning are accompanied by temperature changes in the body, which in turn affect the temperature of the skin.

Infrared imaging (IR) was shown to be a useful method to diagnose the signs of certain diseases by measuring the local skin temperature. As a new medical infrared imaging technology, TTM can pinpoint the abnormal heat sources inside human body by using thermography analysis through the surface temperature distribution. Since the invention of TTM, it has been applied in disease diagnosis such as oncology (breast, skin, etc.), vascular disorders (diabetes, deep venous thrombosis), and monitoring the efficacy of therapeutic drugs, etc.[32-34]. So, in this trail, we try to assess the dose-effect of moxibustion through combining measurements of the subjective patient-reported scales with objective TTM images.

In conclusion, this study will evaluate the effect difference of long-snake-like moxibustion with 60-minute and 30-minute duration, measured with medical infrared imaging technology—TTM and traditional scales. The result will contribute to the explore of the dose-effect relationship of moxibustion, therefor to optimize efficacy of moxibustion.

Trial status

The protocol number is ChiCTR2000041000. The date of registration was 16 December 2020. The recruitment began on 22 December 2020 and we plan to complete the recruitment on 1st January 2022.

Abbreviations

CFS
Chronic fatigue syndrome; TCM:traditional Chinese medicine; TTM:Thermal Texture Maps; FS-14:Fatigue scale-14; SDS:Self-rating depression scale; SAS:Self-rating anxiety scale; CBT:cognitive behavioral therapy; GET:graded exercise therapy; GV:Governor Vessel; SF-36:Short Form 36 Health Survey Questionnaire; SAS:Statistics Analysis System; CV:conception vessel; SD:standard deviation; CI:certificate interval; CRF:case report form; MRI:magnetic resonance imaging; IR:infrared imaging

Declarations

Ethics approval and consent to participate The trial will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). Research ethics approval was attained from the Ethics Committee of Teaching Hospital of Chengdu University of TCM (NO.2020KL-046). Informed consent will be obtained from each patient.

Consent for publication Not applicable.

Availability of data and materials

Data sharing is not applicable to this study protocol because no datasets have yet been produced. Study materials are available by contacting the corresponding author on reasonable request.

Competing interest*s*

The authors have no conflicts of interest to declare.

Funding

This work is externally supported by the government funding- Science and Technology Support

Program of Science & Technology Department of Sichuan Province (No. 2020YFS0378).

Authors' Contributions

(I) Conception and design: TT Ma, J Wu; (II) Administrative support: J Wu; (III) Provision of study materials or patients: TT Ma, R Gong; (IV) Collection and assembly of data: R Gong; (V) Data analysis and interpretation: R Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Acknowledgments

Not applicable.

Authors' details

[1] Center of Preventive Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China; [2] College of Acupuncture and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China

References

1. Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason L, Bleijenberg G, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Services Research. 2003;3:25-33.
2. Capelli E, Zola R, Lorusso L, Venturini L, Sardi F, Ricevuti G. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An Update. International Journal of Immunopathology and Pharmacology. 2010;23:981-9.
3. Ng S-M, Yiu Y-M. Acupuncture for chronic fatigue syndrome: a randomized, sham-controlled trial with single-blinded design. Altern Ther Health Med. 2013;19:21-6.
4. Takakazu, Oka, Tokusei, Tanahashi, Takeharu, Chijiwa, et al. Isometric yoga improves the fatigue and pain of patients with chronic fatigue syndrome who are resistant to conventional therapy: a randomized, controlled trial. BioPsychoSoc Med. 2014;8:27-35.
5. JR P, E M, E T, V H. Cognitive behaviour therapy for chronic fatigue syndrome in adults [Cochrane review]. Cochrane database of systematic reviews (Online). 2008;3:CD001027.
6. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for

chronic fatigue syndrome (PACE): a randomised trial. The Lancet. 2011;377:823-36.

7. Cauwenbergh DV, Kooning MD, Ickmans K, Nijs J. How to exercise people with chronic fatigue syndrome: evidence-based practice guidelines. European Journal of Clinical Investigation. 2012;42:1136-44.
8. Kim HG, Yoo SR, Park HJ, Son C-G. Indirect moxibustion (CV4 and CV8) ameliorates chronic fatigue: a randomized, double-blind, controlled study. Journal of Alternative & Complementary Medicine. 2013;19:134-40.
9. Shu Q, Wang H, Litscher D, Wu S, Chen L, Gaischek I, et al. Acupuncture and Moxibustion have Different Effects on Fatigue by Regulating the Autonomic Nervous System: A Pilot Controlled Clinical Trial. Scientific Reports. 2016;6:37846-54.
10. Huang L-R. modified long-snake-like moxibustion and acupuncture treatment of Chronic Fatigue Syndrome: a randomized controlled trail [D]. Chengdu: Chengdu University of Traditional Chinese Medicine; 2018.
11. Lu L, Fu J-M, Feng F-Y, Liang J-N, Ji S-L, Ma R. Dose-effect relationship in treatment of chronic neck pain with the direct moxibustion of small moxa cone. Zhongguo Zhen Jiu. 2019;39:734-8.
12. Li H, Sang L, Xia X, Zhao R, Wang M, Hou X, et al. Therapeutic Duration and Extent Affect the Effect of Moxibustion on Depression-Like Behaviour in Rats via Regulating the Brain Tryptophan Transport and Metabolism. Evidence-based complementary and alternative medicine. 2019;2019:7592124-32.
13. Xiao A-J, He L, Ouyang X, Liu J-M, Chen M-R. Comparison of the anti-apoptotic effects of 15- and 35-minute suspended moxibustion after focal cerebral ischemia/reperfusion injury. Neural Regeneration Research. 2018;13:257-64.
14. Zhao J-M, Wu L-Y, Liu H-R, Hu H-Y, Wang J-Y, Huang R-J, et al. Factorial study of moxibustion in treatment of diarrhea-predominant irritable bowel syndrome. World Journal of Gastroenterology. 2014;20:13563-72.
15. Hives L, Bradley A, Richards J, Sutton C, Selfe J, Basu B, et al. Can physical assessment techniques aid diagnosis in people with chronic fatigue syndrome/myalgic encephalomyelitis? A diagnostic accuracy study. BMJ Open. 2017;7:e017521.
16. Twisk FNM. The status of and future research into Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: the need of accurate diagnosis, objective assessment, and acknowledging biological and clinical subgroups. Frontiers in Physiology. 2014;5:109-19.
17. Almutairi B, Langley C, Crawley E, Thai NJ. Original research: Using structural and functional MRI as a neuroimaging technique to investigate chronic fatigue syndrome/myalgic encephalopathy: a systematic review. BMJ Open. 2020;10:e031672.
18. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wallace E. Development of a fatigue scale. Journal of Psychosomatic Research. 1993;37:147–53.
19. Jing M-J, Lin W-Q, Wang Q, Wang J-J, Tang J, Jiang E-S, et al. Reliability and Construct Validity of Two Versions of Chalder Fatigue Scale among the General Population in Mainland China. International Journal of Environmental Research and Public Health. 2016;13:147-56.

20. Ding G-J. the study on the correlation between moxibustion sensation curative effect in treating chronic fatigue syndrome by needling LU7,KI6 combined with modified long-snake moxibustion [D]. Chengdu: Chengdu University of Traditional Chinese Medicine; 2019.
21. Wang W, Russell A, Yan Y. Traditional Chinese medicine and new concepts of predictive, preventive and personalized medicine in diagnosis and treatment of suboptimal health. The EPMA journal. 2014;5:4-12.
22. Care NCCFP. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy) in Adults and Children [Internet]. Nice Clinical Guidelines. 2007;11:281-2.
23. Yancey JR, SM T. Chronic fatigue syndrome: diagnosis and treatment. Am Fam Physician. 2012;86:741-6.
24. Vink M, Vink-Niese A. Cognitive behavioural therapy for myalgic encephalomyelitis/chronic fatigue syndrome is not effective. Re-analysis of a Cochrane review. Health Psychology Open. 2019;6:1-23.
25. Wang T, Xu C, Pan K, Xiong H. Acupuncture and moxibustion for chronic fatigue syndrome in traditional Chinese medicine: a systematic review and meta-analysis. BMC Complementary and Alternative Medicine 2017;17:163-73.
26. Huang P, Deng C-Y, Jiang X-O, Hu X-W. Clinical Observation on Treatment of Chronic Fatigue Syndrome with Deficiency of Heart and Spleen by Long Snake Moxibustion. Bright Chinese Medicine. 2020;35:2028-31.
27. Zheng S-H, Zheng S-Z, Wu Y-J, Jiao J-K, Ren R, Wei L-L, et al. Long-snake moxibustion for treatment of chronic fatigue syndrome with deficiency of both spleen and kidney and its effect on cytokines. Chinese Journal of Traditional Chinese Medicine. 2013;31:2555-62.
28. Crawley E, Collin SM, White PD, Rimes K, Sterne JAC, May MT. Treatment outcome in adults with chronic fatigue syndrome: a prospective study in England based on the CFS/ME National Outcomes Database. QJM: An International Journal of Medicine. 2013;106:555–65.
29. Roberts D. Chronic fatigue syndrome and quality of life. Patient Relat Outcome Meas. 2018;9: 253–62.
30. Huth TK, Eaton-Fitch N, Staines D, Marshall-Gradisnik S. A systematic review of metabolomic dysregulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis/Systemic Exertion Intolerance Disease (CFS/ME/SEID). Journal of Translational Medicine. 2020;18:198-211.
31. Rivera MC, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review. Diagnostics. 2019;9:91-124.
32. Herman C, Cetingul MP. Quantitative Visualization and Detection of Skin Cancer Using Dynamic Thermal Imaging. J Vis Exp. 2011;51:2679-82.
33. Bauer J, Hoq MN, Mulcahy J, Tofail SAM, Gulshan F, Silien C, et al. Implementation of artificial intelligence and non-contact infrared thermography for prediction and personalized automatic identification of different stages of cellulite. EPMA J. 2020;11:17-29.

34. Murthy JN, Jaarsveld Jv, Fei J, Pavlidis I, Harrykissoon RI, Lucke JF, et al. Thermal Infrared Imaging: A Novel Method to Monitor Airflow During Polysomnography. Sleep. 2009;32:1521–7.

Tables

Table 1
The Symptoms Scale of spleen-kidney Yang deficiency

Variables		Grating criteria	Score
Primary	cold limbs	0: none	
		2: mild and sometimes occurs	
		4: moderate and always occurs	
		6: severe for most of time	
	fatigue	0: none	
		2: mild and sometimes occurs, a little difficult to carry out daily activities	
		4: moderate and always occurs, difficult to carry out daily activities	
		6: severe for most of time, can not carry out daily activities	
	breath shortness	0: none	
		2: mild and sometimes occurs	
		4: moderate and always occurs	
		6: severe for most of time	
	poor appetite	0: none	
		2: mild, less than 1/4 reduction in food intake	
		4: moderate, 1/4 to 1/2 reduction in food intake	
		6: severe, more than 1/2 reduction in food intake	
	weakness of lower back or knees	0: none	
		2: mild	
		4: moderate	
		6: severe	
Secondary	lower back cold pain	0: none	
		1: mild	
		2: moderate	
		3: severe	
	stomach or abdomen fullness	0: none	

Variables		Grating criteria	Score
		1: mild	
		2: moderate	
		3: severe	
	loose stool	0: none	
		1: mild, 1 time/day	
		2: moderate, 2 times/day	
		3: severe, 3 times/day	
	frequent night urination	0: none	
		1: mild, 2 time/night	
		2: moderate, 3–4 times/night	
		3: severe, 5 times/night	
total			