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Research Article

Self-Applied Acupressure and Online Qigong for Chronic Fatigue Post Covid19 (ACUQiG) - Design and Methods of a Randomized Controlled Trial

Theresa Bauer[1], Miriam Ortiz[1], Judith Bellmann-Strobl[2,6], Ute Engelhardt[4], Rainer Nögel[4], Josef Hummelsberger[4], Andreas Michalsen[1], Stephanie Roll[1], Weronika Grabowska[1], Barbara Stöckigt[1], Hosnya Karim[1], Anna Mietzner[5], Carmen Scheibenbogen[2], Stefan N. Willich[1], Friedemann Paul[3,6], Benno Brinkhaus[1], Joanna Dietzel[1*]

[1]Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany

[2]Institute of Medical Immunology, Charité - Universitätsmedizin Berlin, Germany

[3]NeuroCure Clinical Research Center, Charité - Universitätsmedizin Berlin, Germany

[4]International Society for Chinese Medicine (SMS), Munich, Germany

[5]TCM-Praxis-Mietzner, Seelingstr. 32, 14059 Berlin, Germany

[6]Experimental and Clinical Research Center, a cooperation between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité - Universitätsmedizin Berlin, Germany

***Corresponding Authors:** Joanna Dietzel, Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Luisenstr. 57, 10117 Berlin, Germany.

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Abstract

Background: Observational studies confirm the high incidence of postCOVID-19-syndrome (PCS) after infection with SARS-COV2, which can occur in 10-15% of all infected person. A substantial percentage of PCS patients convert into Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS). The aim of this study is to investigate effects of a combined therapy of acupressure and Qigong on parameters of fatigue in patients with PCS. **Methods:** ACUQiG is an open, two-arm randomized controlled single center trial with mixed methods approach. The intervention group (n=100) receive a daily self-massage of selected acupressure points over 8 weeks and follow twice weekly a live online Qigong course over 8 weeks whereas the control group (n=100) is a waiting-group. All patients continue routine care and receive advice on Complementary and Alternative Medicine (CAM). The primary outcome will be the change in the physical function subscale from the SF-36 at week 8. Secondary outcomes at week 8 and week 16: fatigue severity, post-exertional-malaise severity, disease-related quality of life, depressiveness, headache, sleep quality, hand grip strength, lung function, heart rate analysis during orthostasis, and neurocognitive outcomes regarding concentration and attention. A nested qualitative study will be performed with 10 - 12 patients about subjective experiences of the disease and the expectations, experiences and perceived effects of the interventions. **Expected Outcomes:** The results of this study will show if patients with PCS could benefit from a combined therapeutic intervention consisting of self-applied acupressure and Qigong when added to routine care and CAM advice.

Trial registration: Clinicaltrial.gov identifier: NCT05289154, https://clinicaltrials.gov/ct2/show/NCT05289154. First registered 21.03.2022.

Keywords: Chronic fatigue; Post COVID syndrome; Long COVID; Acupressure; Qigong; Randomized controlled trial; COVID-19

Abbreviations

ACUQiG- Trial: Acupressure and Qigong for PCS; AE: Adverse Event; ANCOVA: Analysis of Covariance; CAM: Complementary and Alternative Medicine; CCC: Canadian Consensus Criteria; CFQ: Chalder Fatigue Questionnaire; CM: Chinese Medicine; DMC: Data Monitoring Committee; DSQ-PEM: DePaul Symptom Questionnaire – Post Exertional Malaise; EQ-5D-5L: Questionnaire "disease-related quality of life"; FAS: Full Analysis Set; FEV: Forced Expiratory Volume; FVC: Forced Vital Capacity; ITT: Intention-To-Treat; MCID: Minimal Clinically Important Difference; ME/CFS: Myalgic Encephalomyelitis / Chronic Fatigue Syndrome; PCS: Post COVID Syndrome; PEM: Post Exertional Malaise; PGIC: Patients' Global Impression of Change; PHQ-9: Patient Health Questionnaire 9; POTS: Postural Tachycardia Syndrome; PSQI: Pittsburgh Sleep Quality Index; SAE: Severe Adverse Event; SAP: Statistical Analysis Plan; SF-36: Short Form 36; VAS: Visual Analogue Scale.

Introduction

Background and rationale

International observational studies confirm the high incidence of post-infectious residual syndrome after infection with SARS-CoV2, which can occur in 10-15% of all infected persons, regardless of the severity of the acute infection [1-3]. WHO defined the postCOVID-19-syndrome (PCS) as ongoing symptoms >12 weeks after infection impairing daily activities. PCS patients describe as most common symptoms fatigue, memory and concentration problems, dyspnea, sleep disturbances, joint pain and anxiety or depression [4].

A substantial percentage of 50% of patients with PCS convert into Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS), which often manifests after a viral or bacterial infection [3].

It seems justified to consider effective strategies for the treatment of ME/CFS also in the treatment of PCS, such as acupuncture, moxibustion, Qigong, pacing, yoga, cognitive behavioral therapy, etc. [5,6]. Ongoing clinical studies have been registered in major registries to investigate acupuncture or laser-acupuncture for Long COVID and PCS.

Acupressure is the needle-free method of Chinese Medicine (CM) method acupuncture to stimulate acupuncture points by pressure of e.g., a fingertip and can be applied by patients themselves. Repetitive treatments are necessary in acupressure as in acupuncture in chronic diseases. The self- applicability was of special interest in a patient group that is too fatigued to be motivated to visit a study center for repetitive appointments. Acupressure has been evaluated and shown to be effective in other forms of fatigue and other conditions [7-12]. Qigong is a physical and relaxing exercise with emphasis on deep breathing combined with visualization and slow movements which is used in CM for therapeutic purposes and prevention. Results of small clinical trials have indicated that Qigong could be beneficial in treating ME/CFS [13,14]; ongoing studies registered in clinicaltrials.gov use Qigong for the treatment of acute COVID and the recovery period [15-17].

Routine care in PCS is not established yet, patients are desperate, and practitioners prescribe various off – line therapies and include supplements and strategies from complementary and alternative medicine (CAM) options such as phytotherapy- providing thus an integrative medical approach [18]. Moreover, patients make therapeutic decisions based on anecdotal information transmitted in self- help groups, often including herbs and supplements or meditation. Data on self- help strategies plus various off- line prescriptions are scarce. In this trial - similar to clinical trials investigating rehabilitation programs - we chose a combined study intervention of acupressure plus Qigong as add on to routine care including CAM strategies.

Objectives

The aim of this study is to offer patients suffering from PCS a combined treatment of daily self- applied acupressure and twice weekly Qigong courses over 8 weeks on top of routine care and self-care- strategies from CAM and to evaluate the effects on symptoms of PCS.

Trial design

The ACUQiG study is an open two-arm (parallel groups) randomized controlled single center investigator-initiated trial with mixed methods approach. For ethical reasons and in order to increase recruitment within the trial we offered all patients including the control group a guidebook with CAM symptomatic treatment for the symptoms of PCS. The qualitative substudy with semistructured interviews was added in order to address subjective experiences of PCS, usual care, and the therapeutic study intervention, as well as their expectations of the treatment in a small sample of patients. This qualitative data can complement and deepen the quantitative results.

Methods: Participants, interventions, and outcomes

Study setting

The study will take place in the outpatient clinic for complementary medicine at the Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Germany. Due to the design of the study including an online and self-applied intervention, patients can be recruited from all over Germany.

Eligibility criteria

Inclusion criteria

Patients suffering from chronic fatigue, following a SARS-CoV2 infection (documented by PCR testing or SARS-CoV2-antibodies) which occurred a minimum of 12 weeks before inclusion, aged 18-60 years. At least 3 of the following 7 symptoms have to be present at the time of inclusion and will be assessed by a physician at the screening examination prior to trial enrollment and via validated questionnaires on the following disease burdens: sleep disturbance, headache, joint pain/muscle pain, anxiety/depression, memory/concentration impairment, post exertional malaise, or dysosmia/anosmia, physical capacity of at most 60 mm on a Visual Analogue Scale (VAS, 0-100 mm); Physical Function subscale of the Short Form- 36 (SF-36) of at most 65 points. Patients need technical equipment to participate in online intervention; they have to give oral and written informed consent for the study participation.

Exclusion criteria

As exclusion criteria are defined (among others): Fatigue present prior to SARS-CoV2 infection; presence of severe post-exertional malaise (7 OR 8 of DSQ-PEM questionnaire AND over 14 hours lasting deterioration of condition); other underlying diseases leading to symptoms of chronic fatigue, such as major depression, oncologic disease, multiple sclerosis, fibromyalgia, or substance abuse; other serious underlying conditions, such as severe pulmonary, cardiac, psychiatric, or infectious diseases, that could interfere with study participation or affect results; ongoing opioid therapy or opioid therapy in the week prior to study entry; chronic use of cannabinoids before or during the study; started or suspended psychotherapy during study participation; female participants: pregnancy or breastfeeding; participation in another clinical intervention study during study participation; ongoing retirement pension procedure or planned claiming of a retirement pension due to disability; planned rehabilitation measures during study participation due to PCS.

Dropout and withdrawal criteria

Each patient will have the right to withdraw from the study at any time. Study participation may be discontinued at the discretion of the physician for the following reasons: the patient is unable to continue the study for physical or psychological reasons; failure to cooperate or comply with study procedures. In the event of repeated serious adverse events related to the study procedures, the entire study may be discontinued at the discretion of the principal investigator.

Study interventions

Acupressure and Qigong

The self-applicable acupressure intervention was developed based on a consensus process with experts. It will be taught to the patients under guidance of a study physician, and it will be practiced using exercise materials such as video instruction and a printed manual. The acupressure scheme is a semi-standardized intervention consisting of 5 obligatory points and a maximum of 2 additional symptom-related points. It has been developed in a consensus procedure together with experts from the International

Society for Chinese medicine, Munich, Germany. The obligatory points are in total the following 9 points (see figure 1):Yintang (which is used to increase focus and against headaches) and bilateral: Large intestine 4 (general analgesia especially headaches, pain in the upper extremities and to support the defense in infectious disease), Pericardium 6 (against tightness of the chest and for regulation of tachycardia, sleeping disorders, anxieties), Stomach 36 (abdominal disorders, used in fatigue and for convalescence), and Spleen 6 (used for abdominal disorders, in fatigue and for convalescence). Depending on the predominant additional symptomatology, two of the following points can be chosen and modified throughout the study participation by the patient according to need: Anmian (sleep disorder), Liver3 (emotional tension, anxieties), Gallbladder 20, (headaches), Gallbladder 34 (limb pain), Governor Vessel 23/24 (anosmia, dysosmia) and Lung 7 (shortness of breath). Over 8 weeks, the acupuncture points will be massaged softly and daily 2 minutes per point with a finger (in total a minimum of 18 min daily). Acupressure duration was chosen based on other acupressure trials, it is sufficient to stimulate acupuncture points and short enough to assure adherence.

In addition, an online guided live Qigong class of 45 minutes duration will be offered twice a week for active participation. The patients will be motivated to practice Qigong alone at least one more time per week. The Qigong intervention was defined in a consensus process with CM experts and consists of 2 subsets of Qigong exercises with different intensities (basic and intermediate). All patients will be advised to start with the basic exercises in a sitting or lying position and will be then taught to perform some simple exercises, mainly from the so-called Crane exercises. The crane exercises focus on balancing the heart-energy, the blood circulation and lungs. They gently stretch ligaments and the spine, using visualizations of a gracefully flying bird; after half of the intervention- time patients will be advised to join the intermediate courses where they will learn to perform more complicated exercises of the Crane Qigong (sitting, standing and walking), more breathing techniques and if necessary, additionally vocalizations of the sounds *hu* and *xie* of the six healing sounds. Patients will perform exercises according to their perceived capacity.

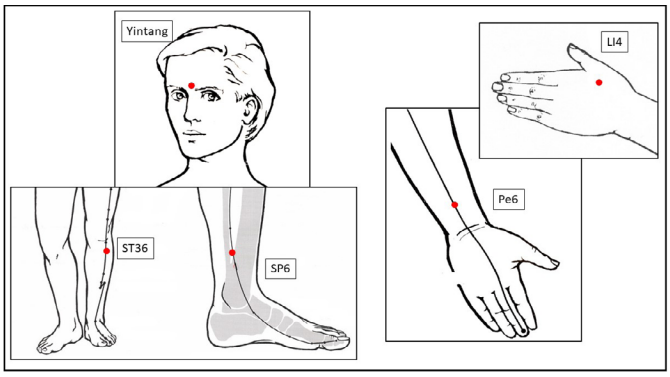

Figure 1: Obligatory acupressure points. WHO nomenclature for acupuncture points: LI4: large intestine 4, ST36: stomach 36, SP6: spleen 6, Pe6: pericardium 6. Modified with permission from G. Stux, Lehrbuch und Atlas, Springer Verlag.

Guidebook for CAM

After randomization patients will receive an existing guidebook for post-viral complaints with self-care measures and recommendations in the area of nutrition, herbs and supplements from western and ayurvedic phytotherapy, traditional Chinese dietetic advices, Kneipp hydrotherapeutic treatments, breathing exercises and relaxation, mind-and-body medicine [19]. The different measures can be chosen and tested independently by the participants.

Control

The control group will receive only the guidebook in addition to routine care. After the completion of the study, this group will receive training videos for acupressure and Qigong with the same points and exercises like the intervention group.

Criteria for discontinuing or modifying allocated interventions

If acupressure is too painful at the acupoint site, or bruising appears, participants will be advised to reduce pressure or spare the single acupressure site with the bruising until it´s dissolution. If Qigong exercises will be too strenuous, patients will be advised to follow the training in a sitting or even reclined position.

Strategies to improve adherence

Patients of both groups will receive diaries, to report the application of strategies from the guidebook, plus in the intervention group the daily application of the acupressure therapy and weekly participation in Qigong sessions. Furthermore, they will note the strategies used from the guidebook. To further maintain adherence all patients will be contacted via telephone in week 2 and week 6 to motivate them to stick to the study interventions.

Relevant concomitant care and interventions

All patients should continue routine care constantly during the study, for example symptomatic therapies such as NSAIDs, sleep medicine or antidepressants, prescribed physiotherapy or ergotherapy, Yoga or meditation. Routine care measures will be reported in the diaries. Additional acupuncture, acupressure or Qigong treatments will be prohibited.

Study outcomes

Primary outcome

The primary analysis of the primary endpoint (exercise capacity, SF-36 Physical Function after 8 weeks) is performed by analysis of covariance (ANCOVA); treatment group (intervention (acupressure+ Qigong) / control) is included in the model as a fixed effect, as well as the baseline value of the SF-36 Physical Function as a covariate. Adjusted group means with 95% confidence intervals and the p-value for the group difference (with significance level 5% two-sided) are presented. The analysis is primarily performed with the Full Analysis Set (FAS) based on the intention-to-treat principle (ITT) without substitution of missing values. All further analyses are considered exploratory, without adjustment for multiple testing. If necessary, a sensitivity analysis will be performed with replacement of missing values by multiple imputations.

Secondary outcomes

Changes in the SF-36 Physical Function subscale between baseline and week 16; changes to baseline of following parameters after week 8 and week 16: severity of fatigue symptoms (CFQ); severity of post-exertional malaise (DSQ-PEM); physical capacity (VAS); sleepiness and sleep quality (PSQI); disease-related quality of life (EQ-5D-5L); depressiveness (PHQ9); headache (VAS); Patient Global Impression of Change (PGIC) at week 8 and 16, physical examination will assess changes to baseline at week 8 and week 16 of handgrip strength (dynamometry), spirometry, blood pressure and heart rate changes in orthostasis and concentration and attention test (d2 test).

Further assessments are planned regarding the adherence to study intervention (acupressure, Qigong, guidebook); satisfaction with intervention (week 8); continuing with intervention (type and frequency) between week 8 and 16; therapy safety by recording adverse events during intervention and until the follow-up in week 16.

Outcomes in detail:

SF-36 Physical Function Subscale [20]

The SF-36 Physical Function subscale is a patient questionnaire and consists of 10 items that cover a hierarchically arranged spectrum of stress (e.g., Lifting or carrying groceries) and can be answered in 3 levels. The item scores (score of 1: yes, severely limited; 2: yes, somewhat limited; or 3: no, not limited at all) are summed to obtain a total score between 0 and 100 [20]. In previous studies investigating ME/CFS the minimal clinically important difference (MCID) was defined as the change of the means of 8 points [21,22], but based on experts opinion a higher value of 10 points has been chosen in this trial.

Chalder Fatigue Questionnaire (CFQ) [23]

The CFQ is a patient questionnaire designed to measure the extent and severity of chronic fatigue in both clinical and nonclinical epidemiologic populations, and is used for various forms of fatigue [3,22,24]. Each of the 11 items is answered on a 4-point scale ranging from asymptomatic to maximally symptomatic, e.g., "Better than usual," "No worse than usual," "Worse than usual," and "Much worse than usual." The respondent's total score can range from 0 to 33 and increases as symptomatology increases. Beyond that, the score includes 2 dimensions - physical fatigue (measured by items 1-7) and psychological fatigue (measured by items 8-11) [23]. The MCID was defined as 2 points difference of the CFQ [21].

Post-exertional malaise (DSQ-PEM) [25]

The DePaul-Symptom-Questionnaire Post-exertional-Malaise (DSQ-PEM) is a questionnaire specifically designed to identify patients with post-exertional Malaise (PEM). It has not been validated for monitoring PEM but will still be evaluated during the follow-ups. The questionnaire consists of 10 questions which are answered by the patient alone or with a physician. There are five questions about physical and mental capacity that can be answered on a 5-point scale (0: not present; 1: sometimes; 2: about half of the time; 3: most of the time; 4: always). Question 6 to 8 refer to deterioration after exertion (yes/no) and question 9 captures the duration of PEM (minimum of 14h for severe PEM). We will define the MCID using the distribution based method (0.5 x Standard Deviation (SD)) of the baseline mean.

Disease-Related Quality of Life (EQ-5D-5L) [26]

The EQ-5D-5L is a patient's questionnaire and consists of five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems,

mild problems, moderate problems, severe problems, and extreme problems. The digits for the five dimensions are combined into a 5-digit number that describes the patient's health status. A specific algorithm converts the 5-digit number into a score [26]. The EQ-VAS captures the patient's self-assessed health status on a vertical VAS with endpoints labeled "The best health status you can imagine" and "The worst health status you can imagine." The VAS can be used as a quantitative measure for health outcomes that reflects the patient's own assessment [27,28]. Based on a former study that defined the MCID of the EQ-5D-5L in stroke patients using two different methods (anchor and distribution based) we define the MCID for the EQ-Index as 0.10 and the EQ-VAS as 8.61 [29].

VAS for physical capacity and headache

The VAS is an established tool for representing pain or global discomfort [30]. By representing it as a horizontal line of 100 mm long it provides an alternative option for the self-assessment of subjective symptoms that has been shown to be a valid and replicable measure [31,32]. The left end indicates no discomfort at all and the right indicating maximum of imaginable discomfort. In our study we used two different VAS's; one for physical capacity (left: no physical capacity at all; right: full physical capacity) and the other for headache (left: no headache; right: worst headache imaginable). The patients should evaluate the average of the last week. Various studies suggest to define the MCID for the VAS of pain at 13mm [33-35]. There are no studies indicating what the MCID for the VAS for physical capacity might be. We will define it distribution based with 0.5 x SD of the baseline mean.

Depression (Patient Health Questionnaire 9 (PHQ-9) [36]

The PHQ-9 is a patient questionnaire in which each of the 9 DSM-IV depression criteria is scored from "0" (not at all) to "3" (almost every day) [36]. Major depression is diagnosed when 5 or more of the 9 criteria for depressive symptoms have been present on at least "more than half of the days" in the past 2 weeks and one of the symptoms is depressed mood or anhedonia. Mild depression is diagnosed if 2, 3, or 4 depressive symptoms were present for at least "more than half of the days" in the past 2 weeks and one of the symptoms is depressed mood or anhedonia. One of the 9 symptom criteria ("thoughts that you would feel better if you were dead or that you would hurt yourself in some way") counts if present at all, regardless of duration. As a measure of severity, the PHQ-9 score can range from 0 to 27, as each of the 9 items can be scored from 0 to 3. A study investigating the depressiveness of patients after spine surgery suggests a MCID of 3.0 for the PHQ-9 [37].

Sleepiness and sleep quality (Pittsburgh Sleep Quality Inventory, PSQI) [38]

The PSQI is a 19-item patient questionnaire in which sleep quality is evaluated within 7 sleep components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (e.g., excessive nodding off) [38]. A cut-off score of > 5 is recommended by the developers to detect poor sleep [38]. The MCID was defined as ≥3 points by the author of the inventory [39].

Patient's Global Impression of Change (PGIC)

The PGIC is a one item scale with 7 levels where the patient can evaluate the global impression of change since the initiation of the study. The levels are representing a dimension from a "very strong deterioration" to a "very strong improvement". Because the PGIC is a subjective measure it is affected unequally by different subjective health domains (e.g. higher correlation with mood and physical activity; lower with pain) [40]. The PGIC is frequently used as a reference for the anchor-based method to define the MCID for other questionnaires [41]. Every amount of alteration or deterioration in this questionnaire is because of a noticeable change for the patients and therefore clinically important. Of course, the higher the variation, the more clinically important it is.

Diaries

The diaries during week 1-8 will evaluate the use of routine care and off-label therapies, such as physical therapies, or plasmapheresis, the adherence to acupressure and Qigong, and to the measures from the guidebook. Questionnaires will assess safety and adverse events (weeks 8, 16), satisfaction with and practicability of the intervention (week 8 and 16), continuation with intervention between week 8 and 16 (week 16) and expectations regarding the effectiveness of the intervention (week 0).

Objective outcome parameters

A physical examination will be performed in a subgroup of 80 patients (40 per group) at baseline, week 8 and week 16. Only patients that will be recruited consecutively outside critical pandemic periods and with residence in Berlin will be considered.

Hand-grip strength

A hand dynamometer will be used to quantify the exhaustibility of muscular effort. It is an established procedure in the evaluation of physical functioning [42] and also has shown to be an effective and objective tool to quantify fatigue or PEM in ME/CFS patients [43,44]. The handgrip force will be measured with a hydraulic dynamometer (Saehan SH5001) with which the maximum and mean force of 10 repeated pulls every five seconds (Fmax1 and Fmean1) will be assessed. A second measurement will take place 60 minutes later (Fmax2 and Fmean2).

Spirometry

Spirometry will be performed to assess residual pulmonary function impairment and respiratory disorders. Various studies have found pulmonary dysfunction following Covid-19 infection

[2,45,46]. In order to assess the forced vital capacity (FVC) or possible obstruction we measure 3 maximum expiratory volumes using the spirometer Vitalograph copd-6 (Vitalograph GmbH, Rellinger Straße 64a, 20257 Hamburg, Germany). The device will provide us with the values of the forced expiratory volume within 1 and 6 seconds (FEV1 and FEV6). The Tiffeneau-Index (FEV1/FEV6) will be calculated by the software.

Orthostasis measurement

The adaptation of heart rate and blood pressure during the change of position from sitting to standing is an indicator for the responsiveness and intactness of the autonomic nervous system. It is established in fatigue research because an association between dysregulation of orthostatic reaction and ME/CFS has been found in various studies [47,48]. Blood pressure and heart rate will be measured while sitting for 2 minutes and after 2, 5, and 10 minutes of standing [3]. Postural tachycardia syndrome (POTS) is defined as an increase of >30 bpm or above 120 bpm over ten minutes of standing [49].

Concentration and Attention Test (Test d2-R) [50]

To assess the dimensions of concentration and attention, the d2-R test has been proven to be a valid instrument, also for the evaluation of cognitive fatigue [51].

The test consists of the letters "d" and "p", which are arranged in 14 rows of 57 characters each and marked with 1 to 4 dashes at the top and/or bottom. The patient's task will be to only cross as many of the "d's" marked with 2 dashes as possible in each row within 20 seconds, producing neither errors of omission nor errors of confusion [50,52].

Individual participant timeline

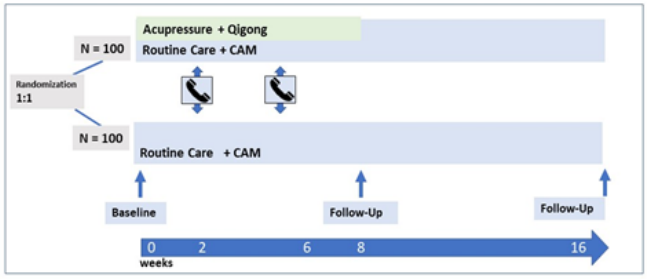

Figure 2: Individual participant timeline of the ACUQiG trial. All patients receive calls at week 2 and week 6 to ensure adherence and to offer counselling for CAM measures. Qigong live online courses and diaries end in week 8, patients can continue acupressure or Qigong courses or CAM measures on their own if desired.

Sample size

The sample size estimate is based on an expected MCID between the treatment groups in the SF-36 Physical Function of 10 points, and a standard deviation of 23 points [53]. With a sample size of 85 patients per treatment group, a two-sided t-test with significance level of 5% has a power of 80%. To compensate an expected dropout rate of approximately 15%, 100 patients per study arm will be randomized. We will continue recruitment until the end of the planned recruitment period, independent of the number of already included patients.

Recruitment

Flyers will be distributed in German doctors' offices and the hospitals of the Charité Universitätsmedizin Berlin, Germany, and further information will be provided via press release on the Internet, in the newspaper and the website of patients' association for PCS. In addition, the study will be advertised in public transport.

Methods: Assignment of interventions

Sequence generation and allocation concealment mechanism

The patients will be randomized by block randomization with a variable block length in a 1:1 ratio into one of the two treatment groups. The computer-generated randomization list (created with SAS for Windows (Version 9.4)) and the allocation to the treatment groups will be displayed for each enrolled patient individually.

Implementation

Each participant allocation will be displayed by the computer program to the study physician who performs the inclusion of patients. The result of the randomization will then be transmitted to the patient who then receives the training materials and course-links.

Blinding

As this is an open study, the patients will not be blinded. An assessor blinding will be used for the data collected during the physical examination (handgrip strength, spirometry, blood pressure and heart rate during orthostasis, concentration and attention test).

Methods: Data collection, management, and analysis

Data collection methods

All data from the electronic case report forms and online questionnaires (from the baseline examination and the questionnaires at baseline, week 8 and week 16), the paper diaries (kept at home by the patients and sent via mail) will be recorded in an online database using pseudonyms or entered directly there by the patients via an individualized study link. Data quality will regularly be controlled. The current data protection regulations of the institute are applied. Corresponding standard operating procedures will be provided.

Plans to promote participant retention and complete follow up

During the telephone contacts in week 2 and week 6 all study participants will be motivated to adhere to the study procedures. After completing the study, patients in the control group will receive the same video-material for acupressure and the Qigong courses.

Data management

Data from the paper-based diaries and questionnaires will be transferred to the online questionnaires of REDCap by authorized study personnel with individualized login information. After checking for correctness and plausibility, all data will be transformed into SPSS data format.

Statistical methods

The data will be analyzed using SAS for Windows, Version 9.4 (SAS Institute, Cary, NC, USA), SPSS (IBM SPSS Statistics for Windows, Version 25, Armonk, NY: IBM Corp) or in R, Version 4.1.2 (R Development Core Team). The analysis of the primary outcome will be performed using analysis of covariance (ANCOVA) with treatment group (intervention (acupressure + Qigong) / control) included in the model as a fixed effect, and the baseline value of the SF-36 Physical Function as a covariate. Adjusted group means with 95% confidence intervals and the p-value for the group difference will be presented. Analysis will be performed using the FAS based on the ITT principle without imputation of missing values. The significance level is set at 5% (two-sided). All other analyses will be considered exploratory, without the adjustment for multiple testing. Depending on the scale, secondary endpoints will be evaluated exploratory in a similar manner as the primary end point. Safety outcomes will be analyzed descriptively. A statistical analysis plan (SAP) will be finalized before data analysis.

Methods for additional analyses

Exploratory subgroup analyses are planned for the following subgroups: effects on SF-36-PFS, Chalder fatigue scale and PSQI of week 8 and week 16 of patients suffering from PCS >6 months vs. PCS <6 months at baseline, presenting <5 PCS symptoms vs. > 5 PCS symptoms at baseline, post-menopausal at baseline vs. pre-menopausal, male vs. female, severe PEM vs. moderate PEM, baseline use of use of supplements and PCS meds. Subgroups will be analyzed by additionally including the subgroup and the subgroup*treatment interaction term into the model. Further analysis will investigate the influence of high- vs. low- use of CAM during the first 8 weeks on the outcomes SF-36-PFS, Chalder fatigue scale and PSQI.

Data monitoring committee (DMC)

Data will be monitored by the study nurse, the data manager and the trial coordinator for completeness. Since the intervention has a low risk profile, we decided not to install a DMC. Severe adverse events (SAEs) will be reported directly to the principal investigator.

Interim analysis

There will be no interim analysis.

Harms/adverse events

All adverse reactions and adverse events (AEs) will be recorded in patient diaries and the electronic case report forms. In case of SAEs patients will be instructed to contact the study center immediately via the contact info given at trial start. SAEs must then be reported to the principal investigator in less than 24 hours.

Auditing

The study staff meets regularly once a week to discuss study progression and upcoming problems.

Qualitative study part

Approximately 10-12 guided, semi-structured interviews will be conducted with randomly selected patients (approximately 5-6 per group) of the subgroup with physical examination after completion of the intervention and recording of the primary outcome parameters (i.e., after week 8 after the start of the intervention). The sample in qualitative studies should not necessarily be large, but rather diverse and as comprehensive as possible in its complexity and contextuality. Therefore, interviews in both groups will be conducted. A sample size of 10-12 interviews (6 in each treatment group) seems suitable for the explanatory approach of the qualitative study part. The focus of the patient's interview will be on their personal experience of PCS, usual care, and the therapeutic study intervention (acupuncture, qigong, and naturopathic advice), as well as their expectations of the treatment.

Analysis of qualitative data: Interviews will be digitally audio-recorded, pseudonymously transcribed, and progressively coded, categorized, and analyzed. Coding will be inductive (from the data material) and deductive (according to the research question and interview guide). Data analysis will be conducted using MAXQDA® software. Depending on the research results, the number and structure of the interviews can be adjusted according to the explorative requirements of the qualitative analysis.

In a further analysis step, the quantitative and qualitative study results will be triangulated, i.e., related to each other. This

allows the results of the study to be supplemented, extended and deepened, and further hypotheses on the possible effects and experiences to be generated. The mixed-methods approach of this study follows a parallel design (quantitative and qualitative data are collected in parallel). The integration of the quantitative and qualitative data is data- and outcome-based [54].

Discussion

PCS is a debilitating condition that leads to an incapacity to work and leaves patients in an isolated and precarious situation, and societies with a considerable health economic problem. ME/CFS research has not been supported enough in the last decades, which produced a gap in therapeutic options; therapies now missing in the management of PCS. CAM research evaluated some options for ME/CFS in the past which must be re-evaluated for PCS. This trial was developed together with patients suffering from PCS and together with specialists in fatigue research, who all indicated that breathing techniques and meditative elements can lead to reduction of autonomous disorders, such as palpitations. Acupressure has been evaluated before as feasible as self- care intervention and beneficial in the treatment of fatigue [8,9]. It was chosen as therapeutic strategy in this trial for fatigued patients. Meeting their increased need to rest, the intervention was designed to be online and self- applied; this made nation- wide recruitment possible. The choice of the acupressure points was in a consensus process with experts International Society for Chinese medicine, Munich, Germany and inspired by previous research [8,9]. Qigong is a form of physiotherapy with meditative elements and a focus on breathing. It has been used for pulmonary rehabilitation in the past and is useful for patients with a lack of energy [55-57]. Ongoing research investigates the effect of Qigong on PCS patients or patients recovering from COVID-19 pneumonia [15-17]. A combined therapy of acupressure and Qigong was chosen to increase the efficacy and to provide a multimodal approach as it is practiced in CM and other types of CAM. I

There are a large variety of self- help measures in the guidebook and we plan to perform further analysis to evaluate the choices and preferences, and the adherence to the chosen therapies and their possible influence on outcome parameters.

Even though the vitality, social functioning, and physical subscale from the SF-36 questionnaire has been found to be more sensitive and specific in discriminating ME/CFS patients from controls [58], we decided to assess the physical function subscale as it is used as a monitoring parameter and already established in fatigue research [3,21,22]. Furthermore, we decided to complement the patient reported outcomes by objective parameters. We defined the kind of examination according to the study of Kedor et al. from 2022 and added the d2 test of attention. For testing the lung function, we use only the FEV1 and FEV6 as a surrogate for lung function. The FEV6 is used as an approach to the FVC [59]. Even though obstructive issues can be found in patients after an infection with COVID-19, two meta-analyses suggest that diffusion capacity impairment is much more common [60,61]. Our examination will therefore be limited to only assess obstructive disorders. Moreover, the d2 test of attention is also limited to assess the kind of cognitive impairment that comes with attention and concentration problems. Memory problems, which are also often described by patients [62] may not be identified.

Routine care for PCS was not yet established at the beginning of the ACUQiG trial; it will be interesting to evaluate the cross-sectional data of off- label therapies of our baseline; treatments that have been offered to our patients by the health care of this particular period after the COVID19 pandemic or chosen by themselves based on recommendation from their self- help groups for example.

Regarding the trial design and a missing sham intervention two aspects have to be mentioned: with the information found on the internet regarding the exact location of acupuncture points, unblinding is likely. In order to increase the study participation, we decided therefore to offer all patients a CAM counselling and chose the waitlist solution. Furthermore, a sham- controlled design would have increased the sample size considerably and make the research project unfeasible with the existing resources for CAM research.

We are expecting a selection bias in our trial due to the kind of intervention as in Europe CAM is more often used by people with a higher socioeconomic status [63,64] which leads to better health-related behavior and less morbidity [65,66]. Therefore, the cohort of the study may not be representative for all PCS patients. Even though we had to exclude patients with severe PEM from the participation, the results of this study might be of use in future research or therapeutic consideration for the treatment of other forms of chronic fatigue.

Declaration

Ethics approval and consent to participate

The approval has been given June 1st, 2022, by the local ethical board under the number A2/073/22. Oral and written consent is obtained from all patients.

Protocol amendments

The protocol has been amended at the beginning of the trial with an addition of the PSQI. In a second amendment the investigators decided to reduce follow- up calls for the maintenance of adherence from 3 to 2 calls only, for organizational reasons. The same latter amendment contained the extension of the sample size of about 30- 50 participants in order to allow for larger subgroups in the evaluation.

Consent for publication

The publication of the manuscript was consented by all authors.

Confidentiality

Personal information about potential and enrolled participants will be collected in a separate data- base which is kept on a separate server only accessible by the study nurse, data manager and trial coordinator. This data base is secured by password and a specific fire wall during the trial. After completion of the trial the personal data will be deleted.

Funding and competing interests

The trial was partially funded by a research grant for Joanna Dietzel with the number KVC 0/121/2021 by the Karl and Veronica Carstens foundation. The foundation has no influence on the development of trial protocol, or the evaluation of the data. All other authors declare no conflict of interests.

Availability of data and materials

Access to the data have the data manager, statistician, trial coordinator and principal investigator. The data is available on request from the corresponding author.

Ancillary and post-trial care

The study intervention has a low risk profile. Participating physicians, Qigong trainers and trial investigators are covered by their insurance in case of injuries that happen during the examination of the patients or the Qigong exercises. After the trial patients are informed about further training options to continue Qigong.

Dissemination policy

Results will be communicated via publication in a peer- reviewed medical journal.

Authors' contributions

TB and JD wrote the manuscript which has been approved of by all authors; BB, JD, MO, SW, SR, JBS, CS, FP developed concept and methodology, SR developed a statistical plan, RN, JH, AM and UE advised and developed the acupressure and Qigong intervention, BS and HK prepared and conducted the qualitative research.

Plans to provide public access to full protocol, participant-level data, and statistical code

Access to the methods will be given to the public via publication of the in a peer reviewed medical journal public access to participant-level data set will be given upon reasonable request.

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Appendices

Trial status: recruiting, 183 patients on the 12.05.2023

Supplement is spirit checklist

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