Contemporary Clinical Trials 50 (2016) 222–228

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Qigong/Tai Chi Easy for fatigue in breast cancer survivors: Rationale and design of a randomized clinical trial

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ARTICLE INFO

Article history:
Received 20 March 2016
Received in revised form 8 August 2016
Accepted 9 August 2016
Available online 16 August 2016

Keywords:
Fatigue
Qigong
Tai Chi
Breast neoplasm
Survivor symptoms

ABSTRACT

Introduction: Breast cancer survivors (BCSs) often report fatigue that persists for years following treatment. Despite a growing body of evidence for meditative movement practices to improve symptoms among BCSs, few studies have explored using Qigong/Tai Chi to reduce fatigue. Additionally, few have examined the biological mechanisms through which fatigue may be reduced using Qigong/Tai Chi.
Methods/study design: We will recruit 250 fatigued, post-menopausal women diagnosed with breast cancer (stage 0-III), between 6 months and 5 years past primary treatment and randomize to a standardized Qigong/Tai Chi Easy (QG/TCE) intervention, a "sham" Qigong group (movements without a focus on the breath and meditative state) (SQG), or an educational support (ES) group. The primary outcome (fatigue), secondary outcomes (anxiety, depression, sleep quality, cognitive function, physical activity), and a biomarker of HPA axis dysregulation (diurnal cortisol) will be assessed at baseline, post-intervention and 6 months postintervention, and biomarkers of inflammation (IL1ra, IL6, TNFα and INF_{γ}) at pre/post-intervention. We hypothesize that QG/TCE will reduce fatigue (and improve other symptoms associated with fatigue) in BCSs experiencing persistent cancer-related fatigue more than SQG and ES. Biomarkers will be examined for relationships to changes in fatigue.
Conclusions: Findings from this study may reveal the effects of the unique mind-body aspects of QG/TCE on fatigue in BCSs with a complex design that separates the effects of low-intensity physical activity (SQG) and social support/attention (ES) from the primary intervention. Further, results will likely contribute greater understanding of the biological mechanisms of these practices related to improved symptoms among BCSs.

1. Introduction

Increasing rates of breast cancer along with improvements in prognosis means the number of survivors is growing across all US populations, regardless of race, ethnicity, and socio-economic status. Of the14.5 million cancer survivors in 2014 (representing 4% of the population), female breast cancer specifically represents 41% of female survivors [1]. Fatigue is nearly ubiquitous as a complaint of patients undergoing treatment for breast cancer [2,3], and has been associated with surgery, chemotherapy and radiotherapy across stages [4], with or without complications of anemia [5]. Cancer-related fatigue has been defined by the National Comprehensive Cancer Network as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" [6]. The etiology of cancer-related fatigue is thought to be a complex biopsychosocial response to diagnosis, treatment, comorbidities, and stress. Fatigue has been shown to persist well past the period of treatment for breast cancer in women who are disease-free, with estimates of 36%–56% being affected three to 10 years past treatment [7–9], and has been shown to have an important and clinically significant association with depression and anxiety [10]. In addition, it is known to profoundly reduce quality of life (QoL) [11] including social, psychological, functional and even financial wellbeing [12].

Exploration of complementary options such as meditative movement (MM) (e.g., Yoga, Tai Chi, Qigong) is common and continues to grow among cancer survivors. MM can be defined as any practice that combines body movement or postures, a focus on the breath, and a meditative state to cultivate deep relaxation [13] and has been shown to improve a wide range of symptoms [14,15]. Specifically in the case of breast cancer survivors (BCSs), yoga has been the most studied of MM practices, showing benefits for fatigue, sleep, anxiety, depression and QoL [16–22]. Qigong and Tai Chi (two forms of MM with similar roots and practice components) have recently been shown to reduce fatigue in cancer survivors; a Qigong intervention for prostate cancer survivors showed reductions in fatigue and distress [23], and Tai Chi reduced fatigue in BCSs [24–27].

A growing body of literature suggests the potential for Qigong and Tai Chi to improve fatigue, as well as QoL, emotional distress, and cognitive function in cancer patients/survivors in general [28,29]. However, no large-scale studies have specifically examined Qigong and Tai Chi effects on fatigue in BCSs. In our pilot work [30] the effects of Qigong/Tai

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http://dx.doi.org/10.1016/j.cct.2016.08.002
1551-7144/

Chi Easy (QG/TCE) - a standardized set of repeated common Qigong and Tai Chi movements - were compared to a "sham" control group (gentle movement and stretching exercises designed to match intensity of movement with the QG/TCE group, without the focus on breath and meditative state) on BCSs. The QG/TCE group showed significant reductions in fatigue compared to control; other factors assessed (depression, sleep quality, cognitive function) were improved, but not significantly more than the sham control, suggesting the need for a more rigorous, fully powered study. The procedures and methodology of a five-year, multi-site randomized controlled trial that investigate the comparative efficacy of a QG/TCE intervention for fatigued BCSs will be described.

This study is funded as a grant (1RO1CA182901-01A1) by the National Institute of Health/National Cancer Institute (NCI) (Clinicaltrials.gov Identifier: NCT02690116).

2. Materials and methods

The purpose of this three-armed randomized controlled trial is to test whether a 12-week QG/TCE, (based on a standardized and tested QG/TCE protocol), is more efficacious for improving fatigue and associated symptoms in women after treatment for breast cancer than control interventions. Two comparison groups will be used; an active, low-intensity sham Qigong (SQG) group, and a non-active educational support (ES) group. These treatments allow for separation of effects associated with gentle exercise alone (controlled in SQG) and education/social support alone without movement (controlled in ES) relative to the MM practice of QG/TCE, to distinguish unique effects of the meditative and breath foci. By utilizing a comparison between the MM intervention and the two control groups, this study plans to increase what is known about the specific subtleties of MM on fatigued BCSs compared to a non-meditative SQG active intervention and a non-active ES intervention. Psychometrics and biomarkers related to fatigue and associated symptoms will be examined before and after the intervention (with a follow-up at six months post baseline) to further understand the mechanisms associated with effects of QG/TCE as distinct from SQG and/or ES.

2.1. Participants

Participants for this study will include 250 women who have completed treatment for breast cancer. *Inclusion criteria* are: 1) diagnosis of stage 0 - III breast cancer; 2) six months to five years past primary treatment; 3) 45–75 years of age; 4) post-menopausal status; and 5) currently experiencing fatigue symptoms (scoring ≤50 on vitality scale of SF-36) [31,32].

Exclusion criteria are: 1) inability to stand for 10-min segments; 2) individuals whose current health status includes fatigue-related factors (hypothyroidism, anemia, uncontrolled diabetes, auto-immune disorders); 3) individuals whose non-cancer related life conditions may contribute to fatigue symptoms, such as currently working night-shift; or use of more than two alcoholic beverages daily; 4) individuals with current, prescription use of oral antihistamines, cyclosporine, and/or corticosteroids; 5) individuals who have substantial experience with a MM practice (i.e., have practiced consistently across three consecutive months in the past year); and 6) individuals who report moderately severe or greater depression.

2.2. Screening assessments

2.2.1. Fatigue

The vitality scale (4 *items from the Medical Outcomes Survey, SF-36*)[99,100] will be used to screen for fatigue, with score ≤ 50 required for inclusion, indicating moderate to severe fatigue.

2.2.2. Moderately severe depression

The Patient Health Questionnaire-9 (PHQ-9) is a self-reported depression scale which contains 9 items querying experience in the past 2 weeks on a Likert-style scale. Scores can range from 0 (absence of any depression-related symptoms) to 27 (major depression). PHQ-9′s internal reliability is excellent with a Cronbach's alpha score = 0.89. A score of 15 or higher (moderately severe) [33] will exclude a potential participant from the study; a referral to a psychiatric support services will be made for anyone identified in this range or anyone indicating risk of self-harm.

2.3. Recruitment

Institutional Review Board approval for this study was received at a large state university. Recruitment will occur in cohorts based on rolling intervention start dates over three and a half years, with each 12-week intervention separated by a three-month period for recruitment activities and data collection. For each cohort, we will recruit 30–36 participants to be randomized to the three arms of the study (10–12 participants per arm).

Female BCSs will be recruited across a large county in the Southwest, primarily through two hospital systems (both with breast clinics) and from a number of community groups, churches, and health fairs targeting cancer, including patients from a range of racial/ethnic and income brackets. One of the participating hospitals provides care to larger proportions of Latino, African American and American Indian patients than other hospitals in the county, and we will aim to recruit/over-recruit from these populations for robust minority representation in the study. Methods of recruitment will include referrals from physicians (oncologists, surgeons, and internal medicine), mailings from hospital partners to eligible women, research team member visits to tumor board reviews, oncology practices, breast cancer support groups, community centers and events, and cultivating coverage in local media outlets.

2.4. Screening and consent procedures

2.4.1. Primary eligibility assessment phone call

Interested individuals will contact the study staff using a dedicated phone number or email address that will be included in all recruitment materials. The research staff will complete a preliminary eligibility screening via telephone to determine if the patient meets initial eligibility criteria.

2.4.2. In-person eligibility visit

Once the potential participant has confirmed interest and passed the primary eligibility phone call, she will be scheduled for an in-person visit to collect more sensitive eligibility-related information (e.g., depression or thoughts of harming oneself), meeting individually with research staff in a private room on the university campus. Final inclusion/exclusion criteria will be evaluated, and if confirmed eligible, the potential participant will receive an informed consent to read and discuss, delineating the purpose of the study, study design, intervention, risks and benefits, and clearly stating that she can withdraw at any time without adverse consequences. Demographic information will also be collected during this visit, including race/ethnicity, level of education, and level of income. Eligible, consented participants will be scheduled for a baseline data collection visit one-week prior to the intervention start date.

2.4.3. Randomization and blinding

Consented participants will be randomized into one of three groups (QG/TCE, SQG, ES) by the study statistician using stratified randomization methods [34] to balance on BMI (high/low) and current physical activity (PA) levels (high/low).

Study staff who will be involved in data collection, entry/cleaning and analysis will be blinded to the participants' group assignment.