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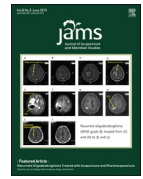
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TECHNICAL NOTES



Methods to Standardize a Multicenter Acupuncture Trial Protocol to Reduce Aromatase Inhibitor-related Joint Symptoms in Breast Cancer Patients

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Abstract

Robust methods are needed to efficiently conduct large, multisite, randomized, controlled clinical trials of acupuncture protocols. The Southwest Oncology Group (SWOG) S1200 trial is a randomized, controlled (i.e., sham-controlled and waitlist-controlled) trial of a standardized acupuncture protocol for treating aromatase inhibitor (AI)-associated arthralgias in early-stage breast cancer patients ($n = 228$). The primary objective of this study was to determine whether true acupuncture administered twice weekly for 6 weeks, as compared to sham acupuncture or a waitlist control, reduced AI-associated joint pain at 6 weeks as assessed by patient reports. The study was conducted at 11 institutions across the United States. The true acupuncture protocol was developed using a consensus-based process. The true acupuncture and the sham acupuncture

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protocols each consisted of 12 sessions administered for 6 weeks, followed by one weekly session for 6 weeks. The true acupuncture protocol used standardized protocol points, and the standardized acupoints were tailored to a patient's joint symptoms. The similarly standardized sham acupuncture protocol utilized superficial needling of nonacupoints. Standardized methods were developed to train and monitor acupuncturists and included online and in-person training, study manuals, monthly phone calls, and remote quality assurance monitoring throughout the study period. The research staff similarly received online and in-person training and monthly phone calls.

1. Introduction

To date, there have been a limited number of multisite, large-scale randomized controlled trials of standardized acupuncture protocols. In this manuscript, we describe the methods used to develop and maintain quality assurance of an acupuncture and sham acupuncture protocol in a multisite, large-scale randomized sham- and waitlist-controlled trial that tested the effects of a standardized acupuncture protocol on reducing joint pain associated with aromatase inhibitor (AI) use among early-stage breast cancer patients. Aromatase inhibitors are widely prescribed to postmenopausal women for the treatment of hormone-sensitive breast cancer; they are effective and improve disease-free survival [1–6]. However, many women develop joint pain and arthralgias after AI initiation and discontinue AI treatment because of its adverse effects. No treatments have been identified that successfully prevent or treat AI-associated arthralgias.

The results of two previous small trials conducted by our group suggest that acupuncture may be beneficial in treating AI-associated arthralgias. The first study was a waitlist-controlled trial ($n = 21$) of postmenopausal women with AI-associated arthralgias who underwent a 6-week course of full body and auricular acupuncture [7]. Improvements were reported in pain severity, pain-related functional outcomes, and physical well-being with no significant adverse events reported. However, the study was limited because of the small sample size and lack of a blinded control group. The second study was a randomized, blinded, sham-controlled trial of postmenopausal women ($n = 38$) with AI-associated arthralgias who underwent a 6-week course of full body and auricular acupuncture [8]. The sham acupuncture arm utilized superficial needling at nonacupuncture points. The investigators and patients were blinded, but not the acupuncturists. Compared to patients in the sham arm, patients who received true acupuncture reported a 50% decrease in the mean Brief Pain Inventory–Short Form scores. Similar changes occurred with the Western Ontario and McMaster Universities Osteoarthritis scores and the Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) scores. These previous results suggest that acupuncture is an effective and well-tolerated strategy for managing AI-associated arthralgias. However, both previous studies involved a single acupuncturist at a single institution. A large-scale multisite trial is needed to test the effects of a protocol on reducing AI-associated arthralgias among a more diverse population of

patients in a variety of clinical and institutional settings and implemented by multiple acupuncturists with differences in acupuncture training.

Previous multisite acupuncture trials have used standardized protocols and have trained multiple acupuncturists to implement the protocol. These studies have included up to 638 patients who were treated at up to 37 institutions [9–15], and the investigator teams trained acupuncturists in person (Karen Sherman and Claudia Witt, personal communication). To our knowledge, previous studies have not developed methods to train and monitor acupuncturists remotely. New robust methods to train acupuncturists to implement clinical trial protocols are needed to efficiently conduct large-scale acupuncture trials.

2. Materials

2.1. Trial design overview

The Southwest Oncology Group (SWOG) S1200 study—officially named, Randomized Blinded Sham- and Waitlist-Controlled Trial of Acupuncture for Joint Symptoms Related to Aromatase Inhibitors in Women with Early Stage Breast Cancer—is funded by the following centers of the United States (US) National Institutes of Health (NIH): National Center for Complementary and Integrative Health (NCCIH), National Cancer Institute (NCI), and Office of Research on Women's Health (R01 AT006376). The study is being conducted within the SWOG NCI Community Oncology Research Program (NCORP) Research Base (1UG1CA189974-01) (www.swog.org/Visitors/AboutUs.asp). The SWOG network includes > 4000 researchers at > 650 institutions, which include 24 NCI-designated cancer centers and additional international cancer centers. The S1200 study is a limited institution trial that is open at 11 institutions, which constitute 28 clinical sites within the SWOG network.

The S1200 study is a 52-week, three-arm trial using a 2:1:1 ratio for true acupuncture, sham acupuncture, and waitlist control, respectively (Fig. 1). Patient randomization is dynamically balanced by the study site to account for potential outcome differences related to discrete acupuncture administration approaches. Two hundred and twenty-eight patients are expected to be recruited.

Patients in the true acupuncture arm receive true acupuncture twice weekly for 6 weeks (i.e., 12 sessions) followed by weekly true acupuncture for 6 weeks (i.e., 6 sessions). Patients in the sham acupuncture arm receive sham acupuncture twice weekly for 6 weeks (i.e., 12

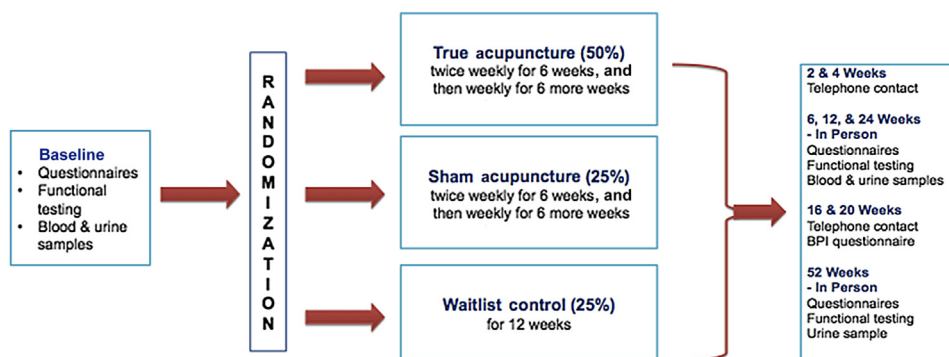


Figure 1 The study schema.

sessions) followed by weekly sham acupuncture for 6 weeks (i.e., 6 sessions). Patients in the waitlist control arm remain in the waitlist condition for the full 12 weeks. As an incentive for trial participation and to increase patients' willingness to be randomized to the sham or waitlist control condition, all patients receive vouchers for 10 true acupuncture "bonus" sessions to be used by the 52 week study visit. Data are collected at baseline, 2 weeks, 4 weeks, 6 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, and 52 weeks (the outcome measures are described below). Patients, study staff, and study clinicians are blinded to the randomization condition (i.e., true or sham condition) of the patients; only the study acupuncturists, the SWOG central statistical center, and one lead site study coordinator (at Columbia University, New York, NY, USA) are aware of the randomization assignment.

2.2. Study objectives

The primary objective of the S1200 trial is to determine whether true acupuncture administered twice weekly for 6 weeks in comparison to sham acupuncture and waitlist control significantly reduces AI-related joint pain in women with early-stage breast cancer, as measured by the Brief Pain Inventory-Short Form worst pain score at 6 weeks. A secondary objective of the S1200 study is to investigate in this study population the effects of true acupuncture administered twice weekly for 6 weeks followed by 6 weekly maintenance treatments, compared to the effects of sham acupuncture and waitlist control. Additional secondary objectives will evaluate the effects of acupuncture on self-reported pain, joint stiffness, quality of life, functional testing, AI treatment adherence, pain medication use throughout the 52-week study period, serum hormones and inflammatory markers, and the safety of acupuncture in this population.

2.3. Eligibility criteria, recruitment, and consent

Eligibility criteria were selected to identify postmenopausal women with a history of early-stage hormone receptor-positive breast cancer who developed or had worsening joint pain and/or stiffness after initiating AI therapy. Ineligibility criteria included women who had underlying joint disease or trauma, who used analgesic medication, or who

had recent exposure to acupuncture that could confound study results. At each clinical site, the clinical and research staff identified and recruited the trial participants. All participants provided written consent. Institutional Review Board approval was obtained by all participating institutions before trial initiation.

3. Procedure

3.1. Acupuncture protocols: True acupuncture and sham acupuncture

3.1.1. Acupuncture protocol development

The acupuncture study interventions were developed by a consensus of acupuncture experts and were based on our previous studies of acupuncture for AI-related arthralgias with adherence to the Standards for Reporting of Controlled Trials in Acupuncture (STRICTA) recommendations [16]. The consensus process involved surveying 12 acupuncturists who had treated oncology patients for at least 5 years. The acupuncturists completed a questionnaire on a variety of treatment principles and acupuncture point protocols, which included open-ended questions on their practice style. The true acupuncture point protocol was then derived by consensus with respect to Traditional Chinese Medicine differential diagnosis, treatment principles, and point prescriptions.

3.1.2. True acupuncture protocol

The true and sham acupuncture treatments consist of 12 sessions lasting 30–45 minutes each that are administered for 6 weeks (i.e., 2 sessions per week) followed by one session per week for the remaining 6 weeks. True acupuncture treatment is semi-standardized. Table 1 displays the true acupuncture point protocol. The point prescription is based on a standard Traditional Chinese Medicine point prescription to treat Bi Syndrome and the National Acupuncture Detoxification Association (NADA) protocol applied to one ear to relieve pain and decrease stress. At every true acupuncture visit, the patients assigned to true acupuncture receive the full body acupuncture prescription and the auricular acupuncture-NADA protocol in one ear (to be alternated at each visit). The needles remain *in situ* for 20–25 minutes. During this time, the study acupuncturist returns to stimulate the

Table 1 True acupuncture protocol.*Full body acupuncture points*

- SJ 5
- LI 4
- GB 41
- GB 34
- ST 41
- KD 3

Auricular acupuncture points

- Shen Men
- Kidney
- Liver
- Upper Lung
- Sympathetic

Joint-specific acupuncture point protocols

Shoulder

- LI 15
- SJ 14
- SI 10

Wrist

- SI 5
- SJ 4
- LI5

Fingers

- SI 3
- Ba Xie
- LI 3

Lumbar

- DU 3
- DU 8
- UB23

Hip

- GB 30
- GB 39

Knee

- SP 9
- SP 10
- St 34

needles once, and utilizes an even needle technique to elicit the *de qi* sensation. In addition, each session includes a joint-specific point prescription tailored for up to four of the patient's most painful joints such as the knees, fingers, lumbar area, shoulders, hips, and wrists. If necessary to access joint-specific points that are inaccessible in the supine position, needles may be inserted after the first set at the proper depth and angle to elicit the *de qi* sensation. The needles are retained for 10 minutes. No electrical stimulation is used. The anatomic site selection may vary between visits, depending on the patient's symptoms.

Stainless steel, single-use, sterile disposable needles are used for the intervention and are inserted at traditional depths and angles. Clinicians are instructed to achieve the *de qi* sensation in which patients experience a dull or achy feeling; this sensation is indicative of effective needling [17]. Needles are re-stimulated manually once during each session. The full body acupuncture needles used are 1 inch, 1.5 inch and 34-gauge, or 3 inches and 30-gauge (manufactured by Tianjin HaingLimSouWon Medical Instrument

Co., Ltd, Beijing, China and distributed by Mac Co., Roslyn Heights, NY, USA). The auricular needles are 15 mm and 38 gauge (SEIRIN-America, Inc., Weymouth, MA, USA).

3.1.3. Sham acupuncture protocol

The number, duration, and frequency of the sessions in the sham acupuncture group are the same as for the true acupuncture group. Table 2 displays the sham acupuncture point protocol. The sham acupuncture point prescription is based on a previous cooperative group study that tested acupuncture versus sham acupuncture for delayed nausea in pediatric patients undergoing highly emetogenic mixed-chemotherapy for solid tumors (Kara Kelly, personal communication; data not published) and based on our previous trials that utilized this sham protocol for the indication of AI-induced arthralgias [8]. The sham protocol consists of a core standardized prescription of minimally invasive, shallow needle insertion utilizing thin and short needles at nonacupuncture points. Joint-specific sham point protocols are also based on the aforementioned criteria and are within the proximity of the specified anatomic area. Preliminary results from our previous studies suggest that there is a difference between deep and localized needling for joint pain commonly experienced by patients with AI-induced arthralgias. Furthermore, we have demonstrated that our sham method does provide adequate blinding among patients [8].

In each session, four standardized points are needed bilaterally and superficially using fine needles (i.e., superficial acupuncture at nonmeridian points). *De qi* and manual stimulation of the needles were avoided. The sham acupuncture protocol also includes joint-specific treatments and an auricular sham intervention that is based on applying adhesives to nonacupuncture points on the ear. Sham acupuncture needles are Mac single-use, sterile disposable needles with a plastic guide tube. The sham acupuncture needles are 0.5 inch 34-gauge needles (Tian Jinhaing Lin Sou Won Medical Instrument Co., Ltd.). The auricular sham product is the Sakamura Magrain Ear Pellet, silver, with pellets removed (Sakamura Lab and Co., Kyoto, Japan). The auricular adhesives are loosely attached and pressed to the sham points on the helix of the auricle, and then removed at the end of the treatment.

3.2. Training acupuncturists and clinical research associates

3.2.1. Prior training of acupuncturists

True and sham acupuncture interventions are provided by licensed acupuncturists and medical doctor acupuncturists licensed with the appropriate state-specific certifications for the site. At the time of study initiation, the acupuncturists were already on staff at the clinical sites or were on staff at community-based clinics affiliated with the cancer center or academic medical center.

3.2.2. Human patient training

All acupuncturists completed human patient training per their institutional guidelines for conducting human research.

Table 2 Sham acupuncture protocol.*Full body acupuncture points*

- Sham 1: On the lateral side of the left forearm near the elbow, 3 cun below the olecranon & 0.5 cun toward the anterior of the small intestine acupuncture meridian.
- Sham 2: On the lateral side of the right forearm near the elbow, 3 cun below the olecranon & 0.5 cun toward the anterior of the small intestine acupuncture meridian.
- Sham 3: At the lower border of the medial condyle of the left tibia, 1 cun anterior & superior to *xi guan* (Liv 7) of the liver acupuncture meridian.
- Sham 4: At the lower border of the medial condyle of the right tibia, 1 cun anterior & superior to *xi guan* (Liv 7) point of the liver acupuncture meridian.

Auricular acupuncture points

- A Sham 1: On the helix of the auricle between the ear apex & helix point #1.
- A Sham 2: On the helix of the auricle between helix point #4 & point #3.
- A Sham 3: On the helix of the auricle between helix point #5 & point #6.

Joint-specific acupuncture point protocols

- Shoulder: On the lateral side of the left or right upper arm, 5 cun below the anterior axillary fold & 1 cun anterior to the Lung acupuncture meridian.
- Fingers/Wrist: On the lateral side of the left & right forearm near the elbow, 5 cun below the olecranon & 0.5 cun toward the anterior of the small intestine acupuncture meridian.
- Lumbar: On the back at the level of thoracic vertebra 8, 5 cun from the center of the spine & 2 cun from the outer channel of the urinary bladder acupuncture meridian; needled bilaterally.
- Hip: On the thigh, approximately 4 cun above the patella & 1 cun away from the anterior of the gallbladder acupuncture meridian.
- Knee: 2 cun above sham 3 or sham 4.

3.2.3. Online training

Adobe Captivate 5 software (Adobe, San Jose, CA, USA; www.adobe.com) was used to develop online training presentations for study acupuncturists. It combines visual, verbal, and video elements. These elements include an introductory module, which covers general information about the study, and two acupuncture-specific modules. An "Introduction to the S1200 study" site training module (10 minutes) includes information on the purpose of the study, information on SWOG study operations locations such as the statistical center and biorepository, the S1200 study sites, the study design and objectives, the basic eligibility criteria, blinding, assessments, patient confidentiality, basic adverse event reporting, and contact information.

Two modules specifically train study acupuncturists. The first acupuncture module (15 minutes) covers data transfer and reporting methods, notification of patient registration and group assignment, documentation of patient visits, treatment frequency and timing, blinding, demeanor with study patients, clean needle technique, and true acupuncture points, materials, and techniques such as pictures and verbal descriptions of the anatomical locations of true body and auricular points used in the study. The second acupuncture module (10 minutes) covers sham acupuncture points, materials, and techniques (e.g., pictures and verbal descriptions of the anatomical locations of the sham body and auricular points used), and videos of the location and needling of each sham body point and methods for sham auricular points.

Each module ended with a short quiz covering information presented in the module. Upon successful completion of the quiz, the acupuncturist sends an electronic mail (i.e., e-mail) message generated by the Captivate 5 program to the coordinating clinical research associate (CRA) at Columbia University.

3.2.4. Training manuals

Written training manuals for acupuncturists were developed and distributed to each site. They cover the same information as in the online training. The manuals are updated throughout the duration of the trial, as needed.

3.2.5. In-person acupuncturist training

At least one acupuncturist from the initial study institutions attended a 4-hour training session at the SWOG conference in San Francisco, CA, USA in April 2012. The session included a study overview presentation for S1200 acupuncturists, CRAs, and other S1200 staff and investigators in attendance. A CRA-specific presentation included a question-and-answer period. During the last 2¹/₂ hours of the training, the study acupuncturists were shown and practiced sham point locations, and needling methods and techniques. Acupuncturists (J.C., A.J.) from the lead site (i.e., Columbia University) also conducted visits to study sites for additional training, as needed. On-site visits last 4–6 hours, depending on the number of acupuncturists at each site. This visit consists of reviewing the training manual, paperwork, and procedures, and providing approximately 1¹/₂ hours of one-on-one training in sham and true treatments for each acupuncturist. Ongoing monthly teleconferences with study acupuncturists, CRAs, and investigators are also conducted to address questions and concerns of the study personnel.

3.2.6. Quality assurance for acupuncturists

To maintain quality assurance for the acupuncturists performing the study procedure for the entire study period, methods were devised for yearly quality assurance training of the study acupuncturists. Quality assurance training includes two separate annual assessments. The first

assessment is a web-based quiz of multiple-choice questions that are related to the study protocol and procedures. The quiz is administered, data are collected, and answers are discussed in an open fashion during the subsequent monthly follow-up teleconference. The quiz answers are also distributed to all study acupuncturists for their reference. The second training assessment is an actual practical demonstration of study procedures with regard to greeting and assessing the study patient, and the acupoint location and needling technique for the true and sham protocols, respectively. The study acupuncturists had the option of performing a live video-based quality assurance session with the lead site's acupuncturist, or performing a recorded video assessment that is sent to the lead site's acupuncturist. An assessment tool using a three-point scoring system (1 = "pass"; 2 = "acceptable, but needs follow up"; and 3 = "unacceptable and needs follow up") is used to assess domains such as greeting, point location accuracy, needle technique, and any other pertinent issues in the protocol and procedures. Table 3 displays the domains assessed by the assessment tool. Acupuncturists scoring a 2 or 3 in any domain are provided additional written, verbal, or video-based trainings with the lead acupuncturist, as needed.

3.3. Randomization and blinding of acupuncture status

Once a patient is enrolled in the trial, they are randomized by the SWOG statistical coordinating center in a 2:1:1 ratio for true acupuncture, sham acupuncture, and waitlist control, respectively. If a patient is randomized to the true

or sham acupuncture condition, the SWOG statistical coordinating center sends an e-mail to the acupuncturists to notify them that a patient has been assigned. The acupuncturist next logs into the SWOG statistical coordinating center website to retrieve the assignment. The acupuncturist is the only member of the site study team that is unblinded to the sham and true acupuncture assignment.

To maintain blinding, the data on the true or sham point prescription administered at each visit will be entered into a separate locked database. It will only be accessible to the study acupuncturists and an unblinded CRA at Columbia University who does not have contact with patients.

3.4. Data collection by acupuncturists

In the S1200 trial, acupuncturists complete a SWOG case report form for each treatment. Case report forms were developed by the study team at Columbia University. The forms include each participant's ID number, initials, date, and the acupuncturist's name and institution. The treating acupuncturist checks boxes to indicate the study session number, the true or sham full body points treated, unilateral point administration, and the unilateral auricular points treated during the acupuncture session. For the true and sham treatments groups, the additional treatment of up to four painful joints is indicated by check boxes.

The S1200 study uses an intent-to-treat analysis. Acupuncturists indicate whether study patients receive fewer acupuncture points than the full study protocol for any reason. Acupuncturists also assist in monitoring protocol adverse events related to the procedures by checking whether the patient reports any bruising, bleeding, infection, needle shock, or other reactions since the previous acupuncture session. Acupuncturists complete and submit each treatment form within 24 hours. To submit forms, acupuncturists scan the form to create an Adobe portable document format (PDF) file on a secure password-protected computer or they fax the treatment form directly to the unblinded CRA at Columbia University. Acupuncturists log onto a SWOG secure file transfer (sFTP) site using a SWOG ID and password, from a preverified Internet provider address. Once logged on to the sFTP site, the PDF file can be dragged and dropped into a site- and patient-specific folder, which is only accessible to the acupuncturists at their institution, and to the unblinded CRA at Columbia University who collects and records the treatment information.

3.5. Current status

The S1200 was activated on March 27, 2012. As of February 16, 2015, a total of 141 patients have been enrolled at 11 clinical sites. There are 33 acupuncturists participating in the trial. Trial accrual is anticipated to close in October 2016.

4. Anticipated result

New robust methods were developed to train acupuncturists and staff to implement a large-scale, multisite randomized sham- and waitlist-controlled clinical trial to test

Table 3 Annual live or video quality assessment domains.

Greeting

- Neutral demeanor
- Greeting for standard first visit
- Greeting for standard follow-up visit
- Inquiry about existing joint pain

Set up

- Clean field technique
- Hand washing
- Point swabbing
- Immediate isolation of used needles

Point location

- Use of bony landmarks
- Use of local anatomy
- Cun measurement

Needles

- Selection of proper needle type
- Selection of proper length

Technique

- Insertion
- Proper technique with tube
- Proper auricular technique
- Proper technique with sham needle
- Stimulation
- Obtaining *de qi*
- Even technique

the effects of a standardized acupuncture protocol on AI-associated joint pain. Novel training methods include online training modules, peer-training, and remote quality assurance monitoring. The trial is underway and trial results are anticipated in 2017.

Disclosure statement

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

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