

Acupuncture Research Protocol: Feasibility of Use of Acupuncture for Treatment of Arthralgia Secondary to Aromatase Inhibitor Therapy in Women with Early Breast Cancers

Byeongsang Oh*^{1,2} PhD
Benjamin Kimble¹ MSc

Anna McLean² BSc
Jane Beith^{1,2} MBBS, PhD

1. Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney, Australia
2. Sydney Medical School, University of Sydney, Sydney, Australia

ABSTRACT

Background: Breast cancer is the most common cancer in females in Australia. Aromatase-inhibitors (AIs) are recommended as adjuvant hormone therapy for postmenopausal women with early breast cancer. A substantial proportion of women taking AIs experience joint pain and stiffness. This AI induced arthralgia does not respond to conventional analgesics and can greatly reduce a woman's quality of life. Studies have suggested that acupuncture may be effective in treating osteoarthritis. **Method:** This is a randomised double blind phase 2 pilot trial. Participants will be randomised to receive sham or electroacupuncture (EA). Participants in the real electroacupuncture group will receive electroacupuncture twice weekly for six weeks. Patients in the placebo group will receive sham electroacupuncture for the same duration of time via specially designed non-skin penetrating needles placed at points close to the real acupuncture points in the study. Outcomes of joint pain and stiffness will be measured with BPI-SF, WOMAC, quality of life and cognitive function with FACT-G, FACT-Cog, hand strength by a grip test, and serum markers of inflammation (CRP) by a blood test. **Discussion:** In this article, we report the acupuncture pilot study protocol and design of a randomised clinical trial to reduce joint pain caused by chemotherapy. We expect this pilot study will provide information about the potential efficacy of acupuncture on arthralgia caused by aromatase inhibitor chemotherapy for women with breast cancer. Further, if this study's results are positive, the data will be used to support grant applications to conduct a large RCT to provide the scientific evidence of acupuncture on arthralgia. **Trial registration:** This clinical trial obtained ethics approval from the Royal Prince Alfred Hospital, Sydney and is registered with The Australian New Zealand Clinical Trials Registry (ANZCTR).

KEYWORDS acupuncture, cancer, pain, randomised clinical trial, research protocol.

* Correspondent author; e-mail: byeong.oh@sydney.edu.au

Introduction

Breast cancer is the most common cancer in women with over 13 000 women being diagnosed each year in Australia.¹ Approximately 75% of patients diagnosed with breast cancer will have hormone-receptor positive breast cancer. Tamoxifen or aromatase-inhibitors (AIs) are currently used as adjuvant hormone therapy for postmenopausal women with endocrine sensitive early breast cancer. While tamoxifen has long been considered to be the gold standard, studies have shown that AIs instead of, or given sequentially to, Tamoxifen have improved disease-free survival. This has led to the American Society of Clinical Oncology (ASCO) guidelines recommending that an AI be included in the management of postmenopausal women with hormone sensitive breast cancer. The use of AIs in the adjuvant setting has increased dramatically worldwide.² However, recent large adjuvant trials of AIs for breast cancer treatment, both clinical and community based, have indicated that 20 to >40% of women taking AIs experience joint pain and stiffness.³

AI induced arthralgia often does not respond to conventional pain medication and can greatly reduce a patient's quality of life.⁴ Also it has the potential to lead to discontinuation of AI treatment. This is of particular concern as the success of AIs as adjuvant treatment depends on a patient's willingness to adhere to long-term treatment.⁵ The mechanism of AI-related arthralgia is currently unknown, but may be related to oestrogen deprivation and the release of proinflammatory cytokines.³

The use of complementary and alternative medicine (CAM) is increasing, with two-thirds of breast cancer survivors⁶ and up to 55% of women undergoing chemotherapy for breast cancer reporting use of CAM.⁷ An increasing proportion of the population believes CAM is a safer alternative for non-life threatening conditions even though its mechanisms of action remain inconclusive.⁸ Acupuncture is one such alternative technique currently used for treating a variety of conditions, including musculoskeletal pain. The analgesic mechanism of acupuncture is uncertain, but it is speculated that analgesia may be mediated by the release of opioid peptides and serotonin.⁹ Previous randomised trials have found that acupuncture can reduce pain in patients with osteoarthritis of the knee.¹⁰ This study will investigate the feasibility of using acupuncture to reduce AI related arthralgia in postmenopausal women with early stage breast cancer.

Aim

The primary objective of this study is to evaluate the feasibility and safety of using electroacupuncture to treat AI induced arthralgia. The secondary objective is to assess any benefits from the use of electroacupuncture for reducing AI induced arthralgia.

Hypothesis

We hypothesise that electroacupuncture will be well-tolerated and may reduce AI related joint pain and stiffness, therefore improving the quality of life of the patients.

Study design

This study is a randomised double-blind phase 2 pilot trial. The total study duration for each participant will be 12 weeks. Participants will be randomised to receive either sham or real electroacupuncture. Participants will receive treatment twice a week for six weeks. Sham acupuncture will be delivered via specially designed non-skin penetrating devices placed at points close to the real acu-points in the study. Surveys to assess pain, stiffness and physical function, immunological tests for inflammatory cytokines and measurement of grip strength will be performed before and after the six weeks of acupuncture and six weeks after completion of acupuncture.

Study population

Inclusion criteria were:

- women who are postmenopausal with a history of stage I, II or IIIa hormone-receptor positive breast cancer and who have been taking a third generation aromatase inhibitor (anastrozole, letrozole or exemestane) for at least six months.
- women who report ongoing pain and or stiffness in one or more joints, which started or worsened after initiation of AI therapy
- baseline worst pain score on the BPI-SF of ≥ 3 on a scale of 0–10
- age >18 years
- ability to understand English, and
- willingness to sign a written informed consent document.

Exclusion criteria were:

- previous receipt of acupuncture for AI-induced joint symptoms or receipt of acupuncture in general in the six months prior to study entry
- inflammatory, metabolic or neuropathic arthropathies, bone fracture or surgery of an effected extremity during the previous six months
- currently taking steroids (oral or injected) or narcotics, severe concomitant illness, severe coagulopathy or bleeding disorder or dermatological disease within the acupuncture area, and
- patients with cardiac pacemakers, defibrillator or any other implanted or topical electrical device, active infection and needle phobia rendering patient unable to receive electroacupuncture.

Sample size: This study will recruit 15 participants per arm (total $n = 30$).

Research Interventions

Participants in both groups will receive acupuncture consisting of bilateral perpendicular insertion of sterile disposable acupuncture needles (Viva, made in China, gauge and size 0.20mm x 25mm) at various acu-points twice a week (Day One Monday, Day Two Thursday) for six consecutive weeks. During this time patients in both groups will be allowed to take their usual medication, including pain medication as needed and other CAM therapies. The acupuncture protocol and procedures will follow the *Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture* (STRICTA) recommendations and a standardised protocol.¹¹

The designation of acu-points will adhere to the *WHO Standard Acupuncture Point Locations in the Western Pacific Region*.¹² The sites will be LI4 *Hegu*, LI11 *Quchi*, GB34 *Yanglingquan*, ST40 *Fenglong*, LR3 *Taichong*, GV20 *Baihui*, EX-HN1 *Shishencong* and EX-UE9 *Baxie* on Day One and GB21 *Jianjing*, TE5 *Waiguan*, ST6 *Zusanli*, SP6 *Sanyinjiao*, LR3 *Taichong*, GV20 *Baihui*, EX-HN1 *Shishencong* and EX-UE9 *Baxie* on Day Two. Acu-points LI11 *Quchi*, LI4 *Hegu*, GB21 *Jianjing*, TE5 *Waiguan*, EX-UE9 *Baxie* were chosen to improve pain and stiffness of arm and hand. Acu-points GB34 *Yanglingquan*, ST36 *Zusanli*, ST40 *Fenglong*, SP6 *Sanyinjiao*, LR3 *Taichong* were selected to improve pain and stiffness of leg and feet. Acu-points GV20 *Baihui*, EX-HN1 *Shishencong* and LR3 *Taichong* were also selected to reduce stress and improve cognitive function. Research suggests that stimulation of acu-points ST6 *Zusanli*, LI4 *Hegu* may improve immune function.

In the treatment group, the needles will be inserted, with bilateral rotation until the *deqi* sensation is elicited. The needling techniques include twirling, thrusting and lifting. After *deqi* is achieved, the needles will be connected through a microalligator clip and an electrode to a battery-operated pulse generator connected to the negative pole on the acu-points LI4 *Hegu* or TE5 *Waiguan* and a microalligator clip and an electrode connected to the positive pole on acu-points LI11 *Quchi* or GB21 *Jianjing*. Electrical frequency will be delivered over 2–10 Hz, 0.5–0.7 milliseconds duration pulse width for 20 minutes (Electro-Acupuncture Units IC-4107, ITO Co Ltd, Japan). Electroacupuncture methodology was developed based on previous studies conducted with cancer patients.^{3,13}

Patients in the non-active group will receive sham electroacupuncture following the same schedule via specially designed non-skin penetrating devices placed at points close

to the real acu-points in the study. Treatment will consist of bilateral manipulation using specially designed sham acupuncture needles¹⁴ (Asiamed, Pullach, made in Germany; 0.30mm x 30mm) at five acu-points close to the real acu-points. The sham needle produces a pin-point pressure sensation. It does not penetrate the skin and automatically retracts on contact. Care will be taken to avoid a *deqi* sensation. The electroacupuncture machine will deliver the same audiovisual stimuli as in the electroacupuncture treatment arm, but lead wires will be concealed and disconnected so that no electrical current is passed through to the needles.

Two acupuncturists (OB and KB) who have more than 10 years experience in acupuncture practice will provide acupuncture treatment to the participants. One (OB) is a clinical senior lecturer at the Sydney Medical School and has six years of acupuncture training. The other (KB) is an acupuncture clinician who has had six years of acupuncture training with 10 years of practical acupuncture experience. Before the needle insertion, the acupuncturist will evaluate patients according to traditional Chinese medicine diagnostic procedures. However, the acupuncturists will administer the standard electroacupuncture protocol only. The first treatment will take an average of 60 minutes including the traditional Chinese medicine diagnosis. Follow up treatments will take an average of 40 minutes, including evaluation and treatment. All electroacupuncture will be 20 minutes duration per session.

Outcome measurement

All outcomes will be assessed by a research assistant blinded to the treatment arm. Measurements will be done at baseline and within one week of completion of treatment. To ensure a comprehensive evaluation of the patient's symptoms, both self-report and grip strength tests will be utilised. Baseline self-assessment will involve three short questionnaires: the BPI-SF, WOMAC, FACT-G and FACT-Cog, which collectively assess the severity of pain, evaluate the impact on quality of life and determine social and emotional well being, and cognitive function. Participants will also complete a very brief survey on their use and attitudes towards CAM. Hand grip strength will be assessed using a dynamometer which the participant will squeeze three times with maximal force. The average for each hand will be recorded. Throughout the acupuncture program, participants will document any changes in dosage and/or frequency of analgesic use. At the completion of acupuncture treatment, all baseline measurements will be repeated.

Data analysis

Tolerability to the electroacupuncture treatment will be assessed by level of participant satisfaction including compliance with treatments and side effects. Paired independent t-tests will be used to compare pre- and post-treatment values for each of the outcomes measured. In addition, two-sample t-tests will be used to compare the average change in score for the group randomly assigned to receive electroacupuncture with that for the group assigned to receive sham electroacupuncture. The variables (use of pain medication and CAM therapies) will be controlled by a multiple regression model during the statistical analysis.

Discussion

Recently, our study suggested that the use of acupuncture by cancer patients is growing.¹⁵ This pilot study was designed to test the feasibility and efficacy of electro acupuncture for women with breast cancer prior to designing a large randomised clinical trial (RCT). These study results will provide data to calculate appropriate sample size for RCT.

Further, innovative approaches to acupuncture research design are needed. This acupuncture study design needs improvement before an appropriate RCT is performed. The complexity of acupuncture research design has been recognised, but there are no single agreed approaches to overcoming methodological challenges.¹⁶ Currently, the implications and feasibility of a double-blind RCT methodology for the assessment of acupuncture interventions is under debate. The National Institute of Health (NIH) in the USA recommended a three arm design for CAM studies (intervention arm, placebo control arm and usual care control arm) instead of the two arms used in conventional medicine studies (intervention arm, placebo control arm).¹⁷ The three arm design will improve the evaluation of CAM but add significantly increased financial costs of running research projects. Where blinding of treatments is not possible, this must be acknowledged and the inclusion of an attention-control group (in addition to standard care alone) needs to be considered.

In this study, participants will be randomised to receive two sessions per week for six weeks only with standard acupuncture treatment. This is a strength of the study, in terms of the treatment being controlled, but it can also be considered a limitation. The acupuncture may be more effective if patients are allowed to have additional acupuncture points based on the symptoms of individual patients. The design of the study can also be improved with the addition of long-term follow-ups to determine the duration of the efficacy of the acupuncture treatment.

In conclusion, more acupuncture studies with large RCTs are required to prove the efficacy of acupuncture for controlling the symptoms of cancer treatment. When the evidence is available, it will be possible to develop evidence-based guidelines regarding the appropriate use of acupuncture and integrate this evidence with conventional medicine within the health care system.

Research Funding

This study was awarded the Cancer Institute NSW Innovative Grant in 2008 and supported by the Sydney South West Area Health Service, NSW Department of Health.

Clinical Commentary

Use of acupuncture by cancer patients in Western countries is increasing, although supporting evidence is limited. Thus, evidence of acupuncture for cancer care is essential for Chinese medicine practitioners, patients and health care professionals. This clinical trial is design to provide evidence of acupuncture for cancer care as well as to encourage Chinese medicine practitioners to engage in scholarly activities.

References

1. AIHW (Australian Institute of Health and Welfare) & AACR (Australasian Association of Cancer Registries) Cancer in Australia: an overview, 2008. Cancer series no. 46. Cat. no. CAN 42. 2008. Canberra: AIHW
2. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365(9453):60–2.
3. Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *J Clin Oncol* 2010;28(7):1154–60.
4. Coleman RE, Bolten WW, Lansdown M, Dale S, Jackisch C, Merkel D, et al. Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. *Cancer Treat Rev* 2008;34(3):275–82.
5. Hershman DL. Getting a grip on aromatase inhibitor-associated arthralgias. *J of Clin Oncol* 2008;26(19):3120–1.
6. Boon H, Olatunde F, Zick S. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Womens Health* 2007;7(1):4.
7. Navo MA, Phan J, Vaughan C, Palmer JL, Michaud L, Jones KL, et al. An assessment of the utilization of complementary and alternative medication in women with gynecologic or breast malignancies. *J Clin Oncol* 2004;22(4):671–7.

8. Oh B, Butow P, Mullan B, Beale P, Pavlakis N, Rosenthal D, et al. The use and perceived benefits resulting from the use of complementary and alternative medicine by cancer patients in Australia. *Asia Pac J of Clin Oncol*. 2010;6(4):342–9.
9. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002;136(5):374–83.
10. Kwon YD, Pittler MH, Ernst E. Acupuncture for peripheral joint osteoarthritis. *Rheumatology* 2006;45(11):1331–7.
11. MacPherson H, Altman DG, Hammerschlag R, Li YP, Wu TX, White A, et al. Revised standards for reporting intervention in clinical trials of acupuncture (STRICTA): extending the CONSORT Statement. *Aust J Acupunct Chin Med* 2010;5(2):8–22.
12. World Health Organization, editor. WHO Standard Acupuncture Point Locations in the Western Pacific Region. World Health Organization; 2008.
13. Shen J, Wenger N, Glaspy J, Hays RD, Albert PS, Choi C, et al. Electroacupuncture for Control of Myeloablative Chemotherapy-Induced Emesis: A Randomized Controlled Trial. *JAMA*. 2000 December 6, 2000;284(21):2755–61.
14. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;352:364–365.
15. Lu W, Dean-Clower E, Doherty-Gilman A, Rosenthal DS. The value of acupuncture in cancer care. *Hematology/Oncology Clinics of North America*. 2008;22(4):631–48.
16. Kaptchuk TJ, Frank E, Shen J, Wenger N, Glaspy J, Hays RD, et al. Methodological issues in trials of acupuncture. *J Amer Med Assoc* 2001;285(8):1015–6.
17. Linde K, Streng A, Jurgens S, Hoppe A, Brinkhaus B, Witt C, et al. Acupuncture for Patients With Migraine: A randomized controlled trial. *J Amer Med Assoc* 2005;293(17):2118–25.