Acupuncture for treatment of arthralgia secondary to aromatase inhibitor therapy in women with early breast cancer: pilot study

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ABSTRACT

Background Aromatase inhibitors (AIs) are recommended as adjuvant hormone treatment for postmenopausal women with early breast cancer. A substantial proportion of women taking AIs experience joint pain and stiffness. Studies have suggested that acupuncture may be effective in treating joint pain.

Objective A pilot study was conducted to evaluate the feasibility, safety and efficacy of using acupuncture to treat AI-induced arthralgia.

Methods A total of 32 patients were randomised to receive either sham or real electroacupuncture (EA) twice weekly for 6 weeks. Outcomes of joint pain, stiffness and physical function were measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), overall pain severity and interference with the BPI-SF and quality of life (QOL) with the Functional Assessment of Cancer Therapy-General (FACT-G) instrument. Hand strength was assessed by a grip test, and a serum marker of inflammation (C reactive protein (CRP)) was also measured. All assessments were performed at baseline, 6 weeks and 12 weeks, except for blood samples at baseline and 6 weeks only.

Results No serious adverse events were reported during or after acupuncture treatments. There were no significant differences in outcome measures. However, positive trends were observed in stiffness and physical function at week 12 in favour of real EA.

Conclusions Findings suggest that acupuncture is feasible and safe in patients with breast cancer with joint pain caused by AI. A larger study with adequately powered to confirm these results and detect clinically relevant effects is needed.

INTRODUCTION

Breast cancer is the most common cancer affecting women and the second leading cause of cancer death among women in Australia and the USA.1 2 Approximately 75% of breast cancers are oestrogen receptor-positive.3 Tamoxifen or aromatase inhibitors (AIs) are currently used as adjuvant hormone treatment for postmenopausal women with hormone receptor-positive 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.4 This led the American Society of Clinical Oncology (ASCO) to recommend that AI be included in the management of postmenopausal women with hormone receptor-positive early breast cancer.5 The use of AIs in the adjuvant setting has increased dramatically worldwide.5 6 However, recent large adjuvant trials of AIs for breast cancer treatment, clinical and community based, have indicated that at least 20% to 40% of women taking AIs experience joint pain and stiffness.7 The mechanism of AI-related arthralgia is currently unknown, but may be related to oestrogen deprivation and the release of proinflammatory cytokines.7

AI-induced arthralgia often does not respond to conventional pain medication and can greatly reduce a patients’ quality of life (QOL).8 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 patients’ willingness to adhere to long-term treatment.9

The use of complementary and alternative medicine (CAM) by cancer patients is increasing worldwide,10 11 with up to 55% of women undergoing chemotherapy for breast cancer and over 65% of...
breast cancer survivors reporting use of CAM. 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. 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. Thus, we conducted a pilot randomised controlled trial (RCT) of acupuncture in postmenopausal women with early stage breast cancer taking AIs. The primary objective of this study was to evaluate the feasibility and safety of using acupuncture to treat AI-induced arthralgia. The secondary objective was to assess any benefits of the use of acupuncture for reducing AI-induced arthralgia.

METHODS
Participants
This study was conducted at a tertiary teaching hospital. Patients were recruited from medical oncology clinics between June 2009 and August 2011. The study protocol was approved by the Sydney Local Health District Ethics Review Committee at the Royal Prince Alfred Hospital.

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 6 months; report ongoing pain and/or stiffness in one or more joints, which started or worsened after initiation of AI treatment; 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 6 months prior to study entry; inflammatory, metabolic or neuropathic arthropathies; bone fracture or surgery of an affected extremity during the previous 6 months; currently taking steroids (oral or injected) or narcotics; severe concomitant illness; severe coagulopathy or bleeding disorder or dermatological disease within the acupuncture area; patients with cardiac pacemakers, defibrillators or any other implanted or topical electrical device; active infection; and needle phobia rendering a patient unable to receive electroacupuncture (EA).

Randomisation procedure
Patients were randomly assigned to receive either real or sham EA treatment. The randomisation list was computer generated by a researcher not in contact with participants. Serially numbered, sealed, opaque envelopes were used to indicate assignment and prepared by a researcher not in contact with participants. Patients were entered into a log before the envelopes were opened. All envelopes were accounted for.

Outcome measurement
Perceived benefit of acupuncture
Perceived benefits and acceptability of acupuncture were assessed with a purpose-designed instrument.

Brief Pain Inventory Short Form (BPI-SF)
The BPI-SF is an 11-item scale that allows patients to rate the severity of their pain and the degree to which their pain interferes with daily functioning. Mean scores of the severity and interference items can be used as measures of pain severity and pain interference, respectively.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
The WOMAC is used to assess pain, stiffness and physical function in patients with osteoarthritis, but has also been used for patients with fibromyalgia. It consists of 24 items divided into 3 subscales of pain, stiffness and physical function. Participants are given a visual analogue that uses anchors of ‘no’ to ‘extreme’ pain, stiffness or difficulty, where higher scores indicate greater pain, stiffness or physical function.

Functional Assessment of Cancer Therapy-General (FACT-G)
QOL was measured with the FACT-G instrument. This well validated and widely used measure is a 27-item patient self-reported instrument designed to measure multidimensional QOL in heterogeneous patients with cancer. The FACT-G consists of four subscales assessing physical well-being (PWB), emotional well-being (EWB), social well-being (SWB) and functional well-being (FWB) with higher scores reflecting a better QOL.

Handgrip strength test
Hand and forearm muscular strength was assessed using a dynamometer, which the participant squeezed three times with maximal force. The average of each handgrip strength was recorded.

Blood analysis
All participants had their C reactive protein (CRP, an inflammatory marker) level and erythrocyte sedimentation rate (ESR) measured at the Biochemistry Department, Royal Prince Alfred Hospital in Camperdown, New South Wales, Australia.

Procedure
Self-reported outcomes and handgrip test were assessed at baseline, 6 weeks (post treatment) and 12 weeks (follow-up); blood samples were collected at baseline and 6 weeks; and perceived benefit and acceptability of CAM was assessed at 6 weeks.

After randomisation, participants received treatment twice weekly for 6 weeks. The acupuncture protocol...
and procedures followed the Standard for Reporting of Control Trial Acupuncture (STRICTA) recommendations and a standardised protocol. An EA methodology was developed based on previous studies conducted with patients with cancer. Participants in both groups received EA consisting of bilateral perpendicular insertion of sterile disposable acupuncture needles (Viva, made in China, gauge and size 0.20 × 25 mm) at various acupuncture points 2 days a week (treatments separated by 2 days) for 6 consecutive weeks. During this time, patients in both groups were allowed to take their usual medication, including pain medication as needed and other therapies (participants documented any changes in dosage and/or frequency of analgesic use). Two acupuncturists (OB and KB) with more than 10 years of acupuncture experience provided acupuncture treatment to the participants. The acupuncturist evaluated patients according to traditional Chinese medicine (TCM) diagnosis procedures before providing the treatment. However, acupuncturists administered the standard acupuncture protocol only. Each treatment session took approximately 30 min, comprising 10 min of consultation and 20 min in which the acupuncture needles were stimulated.

The designation of acupuncture points adhered to the first edition of the Standard Acupuncture Nomenclature (World Health Organization Regional Office for the Western Pacific, 2008). The acupuncture points were LI4, LI11, GB34, ST40, LR3, GV20, Shishencong and Baxie on day 1 and GB21, TE5, ST36, SP6, LR3, GV20, Shishencong and Baxie on day 2. Acupuncture points LI11, LI4, GB21, TE5 and the Baxie extra point were chosen to improve pain and stiffness of the arms and hands. The remaining acupuncture points GB34, ST36, ST40, SP6 and LR3 were chosen to improve pain and stiffness of the legs and feet. Acupuncture points GV20, Shishencong and LR3 are also used to reduce stress levels and improve cognitive function. Research has also suggested that stimulation of acupuncture points ST36 and LI4 can improve immune function.

The needling technique included twirling, thrusting and lifting. In the treatment group the needles were inserted with bilateral rotation until de qi sensation was elicited. The needles were connected through a microalligator clip and an electrode to a battery-operated pulse generator connected to the negative pole for the LI4 and TE5 acupuncture points and the positive pole for the LI11 and GB21 acupuncture points. Electrical stimulation was delivered using pulse width of 0.5–0.7 ms at alternating frequencies of 2–10 Hz, to the maximum comfortable intensity for 20 min (Electro-Acupuncture Units IC-4107, ITO Co Ltd, Tokyo, Japan).

Patients in the control group received sham EA following the same schedule via specially designed sham acupuncture needles (0.30×30 mm Streitberger placebo needle; Asiamed, Pullach, made in Germany). The sham needles do not penetrate the skin and instead automatically retract on contact. This permits experience of pinpoint pressure but avoids causing de qi sensation. The needles were placed at six real acupuncture points (GB21, TE5, LI11, LI4 ST36 and LR3). The EA machine was set to deliver the same audiovisual stimuli as in the EA treatment arm, but lead wires were concealed and disconnected so that no electrical current was passed through to the needles.

Data analysis
Tolerability of the EA treatment was assessed by level of participant satisfaction including compliance with treatments and side effects. Paired t tests were used to compare pretreatment and post-treatment values for each of the outcomes measured. In addition, independent samples t tests were used to compare the average change in score for the group receiving EA with that for the group receiving sham EA.

RESULTS
Participant recruitment and follow-up
Out of 32 participants recruited, 29 completed real EA (n=14) or sham EA (n=15). Reasons provided for dropping out of the study were that they felt the acupuncture was not alleviating pain after two EA sessions (n=1) and conflict with work hours (n=2). No patients experienced major adverse effects with the acupuncture treatment except minor bruising on acupuncture points (n=5).

Demographics
The demographic characteristics of participants are shown in table 1. There were no significant differences between the real EA and sham EA groups in age, ethnicity, education level, Eastern Cooperative Oncology Group (ECOG) performance status, year of cancer diagnosis, alcohol intake, smoking, change of body shape, CAM and acupuncture.

Assessment of masking
Masking of EA treatment was not successful; 73% of participants in the sham group thought they received sham EA compared to 20% of participants in the real EA group (p<0.001).

Change of pain medication
Two participants increased their pain medications during study. However, their pain did not improve significantly from preintervention to postintervention.

Perceived benefit and acceptability of acupuncture
Table 2 shows participants’ perceptions of the benefits and acceptability of the acupuncture treatment. At the end of acupuncture treatment, there were no significant differences in the acceptability of acupuncture
Both groups believed that acupuncture was effective (54% vs 57%, p=0.296) and there were no certain side effects. A high proportion of participants in both groups indicated that they would use acupuncture in future (92% vs 77%, p=0.277).

Outcome measurement
There were no significant differences in joint pain, stiffness and physical function (WOMAC), overall pain severity and interference with daily functioning (BPI-SF), QOL (FACT-G), hand strength or inflammatory markers (CRP and ESR) between the sham and real EA groups. However, trends were observed in stiffness, physical function and total WOMAC at week 12 in favour of real acupuncture, and ESR at week 6 (see figures 1–4).

DISCUSSION
Previous research has suggested that a substantial proportion of patients with breast cancer use acupuncture\(^27\) and that it has the potential to relieve cancer treatment-related side effects.\(^28\) This pilot RCT provides preliminary support for the feasibility and safety of acupuncture for women with AI-related arthralgia. However, it did not find statistically significant differences in AI-related joint pain, stiffness, physical function, pain severity and interference with daily functioning, QOL, hand strength and inflammatory markers (CRP and ESR) between the sham and real EA groups.

The main reasons for the non-significant finding of this study may result from the small sample size and use of a potentially active placebo control group. Another reason for the non-significant findings may be the acupuncture points selected. Our protocol allowed standard body acupuncture points only in order to make the treatment replicable for future studies. A recent study that also used standard acupuncture points to examine the effect of acupuncture in reducing AI-induced musculoskeletal symptoms in patients with breast cancer likewise reported non-significant findings.\(^29\) However, according to acupuncture theory, acupuncture treatment is most effective if patients are allowed to have additional acupuncture points based on individual symptoms. Crew \textit{et al} have reported positive results in treating arthralgia in which the selected acupuncture points included body acupuncture points, auricular acupuncture points and response to acupuncture.

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joint-specific points tailored to the participant’s most painful joint areas.\textsuperscript{7, 30} Therefore, it would be worthwhile to compare the outcomes on arthralgia between individualised treatment and standard treatment in a future RCT.

The non-significant findings may also have occurred because sham/minimal acupuncture is not inert, with real acupuncture and sham/minimal acupuncture shown to induce a significant physiological response in a recent study.\textsuperscript{31} Previous research has shown that any type of sensory stimulus, including tactile, is capable of stimulating multimodal receptors of C-fibre primary afferents that can modulate the limbic system and thus reduce the affective components of pain.\textsuperscript{32} Further, clinical trials that used sham acupuncture controls have suggested that sham acupuncture may be as effective as real acupuncture.\textsuperscript{33–35} Since in our study we used non-penetrating needles at the acupuncture points as sham acupuncture, there is a possibility that the sham acupuncture may have provided sufficient stimulation to evoke a physiological effect. This suggestion is corroborated by an interesting finding of this study, in which patients’ arthralgia symptoms showed a tendency to become worse when acupuncture treatment ceased in the sham and real acupuncture groups.

Figure 1  Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness scores for participants in the sham versus real electroacupuncture (EA) groups across assessment points.

Figure 2  Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function scores for participants in the sham versus real electroacupuncture (EA) groups across assessment points.

Currently, the implications and feasibility of a double-blind RCT methodology with sham acupuncture is under debate. The National Institutes of Health (NIH) in the USA recommend 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 vs placebo control arm). Nevertheless, there is no single agreed approach to overcoming these methodological challenges. A perhaps better approach to explore is focusing on the effectiveness rather than efficacy of acupuncture by comparing active treatment to usual care in an RCT.

Despite the limitations, this study also had a number of strengths. Firstly, this study’s findings are helpful in clarifying the safety of performing acupuncture in risk or affected areas of patients with breast cancer. Previous acupuncture guidelines on breast cancer recommended avoiding needle use in the risk or affected area to reduce the possibility of introducing infection or exacerbating lymphoedema. However, this guideline was controversial because it limits the potential effectiveness of the acupuncture treatment on patients with cancer. Findings from recent studies including our study suggest that use of acupuncture in risk or affect areas is safe when the treatment is

**Figure 3** Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores for participants in the sham versus real electroacupuncture (EA) groups across assessment points.

**Figure 4** Mean erythrocyte sedimentation rate (ESR) levels for participants in the sham versus real electroacupuncture (EA) groups across assessment points.
performed by a qualified acupuncturist.\(^{39-41}\) Secondly, this study provided important data on the effect size and power to appropriately design a larger RCT. This may include a double-blind design and individualised treatment. Thirdly, validated self-report and physiological outcome measures were used for a more robust assessment of the study objectives. Finally, compliance with acupuncture treatment was very high compared to other studies,\(^{7}\) with only three dropouts.

In conclusion, this study provides preliminary evidence that acupuncture study in women with AI-related arthralgia is feasible and safe. It also found that EA was well tolerated and may have the potential to alleviate AI-related joint pain and stiffness, improving the QOL of women with breast cancer. Future RCTs with adequate power and consideration of a double-blind design are recommended to clarify the efficacy of acupuncture on AI-related arthralgia clinical outcomes. This information is important in order to develop evidence-based guidelines regarding the appropriate use of acupuncture and therefore potentially integrate acupuncture safely and effectively with conventional medicine within the healthcare system.

Summary points

- Aromatase inhibitors commonly cause joint pain.
- This pilot study showed that acupuncture is feasible and acceptable.
- No significant effects on joint pain were seen.

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