European Journal of Cancer (2014) 50, 267–276

Available at www.sciencedirect.com

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A randomised trial of electro-acupuncture for arthralgia related to aromatase inhibitor use

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Available online 24 October 2013

KEYWORDS
Acupuncture
Breast neoplasm
Clinical trial
Aromatase inhibitors
Adverse effects
Musculoskeletal
Joint pain

Abstract ***Background:*** Arthralgia is a common and debilitating side-effect experienced by breast cancer patients receiving aromatase inhibitors (AIs) and often results in premature drug discontinuation.

Methods: We conducted a randomised controlled trial of electro-acupuncture (EA) as compared to waitlist control (WLC) and sham acupuncture (SA) in postmenopausal women with breast cancer who self-reported arthralgia attributable to AIs. Acupuncturists performed 10 EA/SA treatments over 8 weeks using a manualised protocol with 2 Hz electro-stimulation delivered by a TENS unit. Acupuncturists administered SA using Streitberger (non-penetrating) needles at non-traditional acupuncture points without electro-stimulation. The primary end-point was pain severity by Brief Pain Inventory (BPI) between EA and WLC at Week 8; durability of response at Week 12 and comparison of EA to SA were secondary aims.

Findings: Of the 67 randomly assigned patients, mean reduction in pain severity was greater in the EA group than in the WLC group at Week 8 (-2.2 versus -0.2, $p = 0.0004$) and at Week 12 (-2.4 versus -0.2, $p < 0.0001$). Pain-related interference measured by BPI also improved in the EA group compared to the WLC group at both Week 8 (-2.0 versus 0.2, $p = 0.0006$) and Week 12 (-2.1 versus -0.1, $p = 0.0034$). SA produced a magnitude of change in pain severity and pain-related interference at Week 8 (-2.3, -1.5 respectively) and Week 12 (-1.7, -1.3 respectively) similar to that of EA. Participants in both EA and SA groups reported few minor adverse events.

Clinical Trial Registration: NCT01013337.

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http://dx.doi.org/10.1016/j.ejca.2013.09.022

Interpretations: Compared to usual care, EA produced clinically important and durable improvement in arthralgia related to AIs in breast cancer patients, and SA had a similar effect. Both EA and SA were safe.

1. Introduction

Arthralgia, or joint pain, is a debilitating side-effect of aromatase inhibitors (AIs) among postmenopausal women with hormone receptor positive breast cancer taking these drugs [1]. Nearly half of AI-users in the clinical setting report arthralgia attributable to AIs [2]. Arthralgia ranks as the top symptom associated with AIs discussed in online breast cancer-specific message boards [3] and often results in poor adherence, or discontinuation [4]. Premature discontinuation negatively impacts disease free and overall breast cancer survival [5].

There is emerging evidence [6] and acceptance [7] for acupuncture, a practice in Traditional Chinese Medicine, as a component of pain management. Many breast cancer patients desire the integration of acupuncture into their conventional cancer care [8] and 60% of National Cancer Institute designated comprehensive cancer centres in the United States (U.S.) recommend acupuncture as an approach for patient symptom management [9]. Despite growing interest from patients and cancer centres, rigorous research is needed to guide its evidence-based integration into cancer care to improve patient outcomes.

A few studies have suggested that acupuncture may be safe and effective for managing AI-related arthralgia [10–12]. However, lack of controls, small sample sizes and high drop-out levels in intervention arms limit the interpretation of these results. Additionally, lack of comparison with usual care makes it difficult to evaluate the clinical relevance of the overall effect of acupuncture for this condition. To more definitively test the clinical effect of acupuncture, we conducted a Phase-II randomised controlled trial (RCT) to evaluate the short term effects and safety of electro-acupuncture (EA) for AI-related arthralgia compared to usual care. We chose EA because animal research has demonstrated its clear physiological effect on the endogenous opioid system (enkaphalin, beta-endorphin and endomorphin) and pain reduction [13]. Our primary hypothesis was that patients receiving EA would have a greater reduction in arthralgia and improved function at Week 8 compared to the Waitlist Control (WLC) 'usual care' group. As secondary aims, we evaluated the durability of response with a repeated measure at Week 12 and evaluated the magnitude of response to sham acupuncture (SA) to inform the design of a future Phase-III trial.

2. Methods

2.1. Study participants

We conducted a three arm RCT (EA, SA and WLC) from September 2009 through May 2012 at the Abramson Cancer Center of the Hospital of the University of Pennsylvania, a tertiary care academic medical centre in Philadelphia. The institutional review board of the University of Pennsylvania approved the study protocol. Eligible patients were women with a history of early stage breast cancer (stages I–III) who were currently receiving an aromatase inhibitor (Anastrozole, Letrozole or Exemestane), had joint pain that they attributed to their AI for at least three months, reported a worst pain rating of at least four or greater on an 11 point (0–10) numerical rating scale in the preceding week, reported at least 15 days with pain in the preceding 30 days and signed the informed consent. We excluded individuals who had metastatic (stage IV) breast cancer or who had a history of a bleeding disorder.

2.2. Study design

Participants were randomly assigned to treatment groups using computer-generated numbers sealed in opaque envelopes. The research coordinator first opened the envelope to inform the subject whether she was randomised to the acupuncture or WLC group. Changing block sizes of three or six were used to ensure a two to one acupuncture versus WLC allocation. Subsequently for the acupuncture group, the treating acupuncturist opened a second envelope using computer-generated numbers at the first acupuncture visit to determine if the subject was to receive EA or SA. All participants were educated on joint pain, staying physically active and continuing with current medical treatments (including prescription and over-the-counter pain medications) as usual. Patients in the WLC were told that they could receive 10 real acupuncture treatments after follow-up. To minimise potential reporting bias, WLC patients were informed that if their arthralgia improved during the waiting period, they could still receive acupuncture for other reasons (e.g. relaxation).

2.3. Electro-acupuncture

Two licensed non-physician acupuncturists with 8 and 20 years of experience, respectively, administered