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Effect of acupuncture on aromatase inhibitor-induced arthralgia in patients with breast cancer: A meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Aromatase inhibitor (AI)-induced arthralgia (AIA) is a common side effect that may lead to premature discontinuation of effective hormonal therapy in patients with breast cancer. Acupuncture may relieve joint pain in patients with AIA. We conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the effectiveness of acupuncture in pain relief in AIA.

Methods: The PubMed, Embase, Cochrane Library, and Scopus databases and the ClinicalTrials.gov registry were searched for studies published before February 2017. Individual effect sizes were standardized, and a meta-analysis was conducted to calculate the pooled effect size by using a random effect model. Pain was assessed using the Brief Pain Inventory (BPI) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 3–4, 6–8, and 12 weeks. Secondary outcomes included disability level, upper extremity function, physical performance, and quality of life.

Results: Five trials involving 181 patients were reviewed. Significant pain reduction was observed after 6–8 weeks of acupuncture treatment. Patients receiving acupuncture showed a significant decrease in the BPI worst pain score (weighted mean difference [WMD]: −3.81, 95% confidence interval [CI]: −5.15 to −2.47) and the WOMAC pain score (WMD: −130.77, 95% CI: −230.31 to −31.22) after 6–8 weeks of treatment. One of the 4 trials reported 18 minor adverse events in 8 patients during 398 intervention episodes.

Conclusion: Acupuncture is a safe and viable nonpharmacologic treatment that may relieve joint pain in patients with AIA. Additional studies involving a higher number of RCTs are warranted.

1. Introduction

Breast cancer is the most prevalent cancer in women and is the second leading cause of cancer mortality [1,2]. Approximately 75% of breast cancer cases are estrogen receptor positive [3]. Aromatase inhibitors (AIs) are one of the routine adjuvant therapies administered to postmenopausal women with estrogen receptor–positive breast cancer. Although third-generation AIs (anastrozole,

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letrozole, and exemestane) have been proven to be effective, up to 50% of patients reported musculoskeletal discomfort [4,5]. The prevalence of premature discontinuation attributable to joint symptoms such as AI-induced arthralgia (AIA) can be as high as 13% [4,5]. The etiology and mechanism of AIA remain unclear. A possible mechanism is bone loss induced by estrogen deficiency, which in turn contributes to arthralgia [6]. AIA symptoms, such as morning stiffness, myalgia, and decreased strength, can be debilitating. Conventionally, AIA is relieved using pharmaceutical treatments such as nonsteroidal anti-inflammatory drugs, prednisolone, or bisphosphonates [7,8]. However, their effectiveness is often limited, and they induce further side effects. Nonpharmacological interventions, such as exercise and yoga, may improve AIA, although these interventions require verification in additional trials [9,10]. Acupuncture, a traditional Chinese therapeutic technique, has been increasingly used for treating musculoskeletal pain. A study showed that the practice of stimulating certain acupoints with needles had analgesic effects in patients with knee osteoarthrosis [11]. Several randomized controlled trials (RCTs) have investigated the use of acupuncture in patients with AIA [12–14]. However, these studies have not provided conclusive results. A recent systematic review suggested that acupuncture is effective in managing AIA symptoms [15]. Nevertheless, the limitation of that review is that it included studies with small sample sizes. A recent meta-analysis also assessed the effect of acupuncture for relieving AIA symptoms, however its results are limited because of inappropriate comparisons in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) dimensions and Brief Pain Inventory (BPI) time points [16]. Therefore, combining the results of these trials by conducting a meta-analysis may strengthen the statistical power of these studies. Hence, we conducted a systematic review and meta-analysis of evidence available to date to investigate the effectiveness of acupuncture approach in relieving AIA in breast cancer patients.

2. Materials and methods

2.1. Inclusion criteria

RCTs comparing the outcome of the application of acupuncture and sham acupuncture in patients with AIA were included in this review. The inclusion criteria were clear definitions of acupuncture and sham acupuncture technique, breast cancer stage, and evaluation of post-treatment pain. We excluded trials that met any of the following criteria: (1) patients received acupuncture treatment within the past 6 months, (2) patients received AI treatment <1 month, or (3) patient cohorts reported in duplicates.

2.2. Search strategy and study selection

Relevant studies published before February 2017 were identified from the PubMed, Embase, Scopus, and Cochrane Library databases. The following Medical Subject Headings terms were used: *acupuncture*, *aromatase inhibitor-induced* OR *aromatase inhibitor-related*, and *arthralgia* OR *pain*. The "related articles" option in PubMed was used to broaden the search scope, and all abstracts, studies, and citations retrieved were reviewed. In addition, we identified other studies by using the reference sections of relevant papers and by corresponding with subject experts. Finally, unpublished studies were collected from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. Our systematic review has been accepted by PROSPERO, an online international prospective register of systematic reviews that is curated by the National Institute for Health Research (CRD42015027546).

2.3. Data extraction

Baseline and outcome data were independently abstracted by 2 reviewers (LC and CCL), and the study designs, study population characteristics, inclusion and exclusion criteria, acupuncture techniques, complications, and post-treatment parameters were extracted. The reviewers' individually recorded decisions were compared, and disagreements were resolved by consulting with a third reviewer (KWT). The authors of the studies were contacted for additional information.

2.4. Methodological quality appraisal

Two reviewers (LC and CCL) independently assessed the methodological quality of each study by using the risk-of-bias method recommended by the Cochrane Collaboration [17]. Several domains were assessed including the adequacy of the randomization, allocation concealment, blinding of patients and outcome assessors, duration of follow-up, information provided to participants regarding study withdrawal, whether intention-to-treat analysis was performed, and freedom from other biases.

2.5. Outcomes

The primary outcomes were the severity of post treatment pain, measured using the BPI, and lower extremity pain, stiffness, and function, measured using WOMAC. The BPI assesses worst pain, pain severity, and pain-related interference, which are scored on a scale of 0–10. The WOMAC measures pain (0–500), stiffness (0–200), function (0–1700), and normalized scores (0–100). The secondary outcomes included the Health Assessment Questionnaire Disability Index (HAQ-DI), Pain Visual Analog Scale (VAS), Functional Assessment of Cancer Therapy-General (FACT-G), Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH), Quick Disability of Arm, Shoulder, Hand (DASH), Physical Performance Test (PPT), quality of life (QOL), and handgrip strength test.

2.6. Statistical analyses

Data were entered and analyzed using Review Manager, Version 5.3 (Cochrane Collaboration, Oxford, England). The meta-analysis was performed according to the PRISMA guidelines [18]. Standard deviations were estimated from the provided confidence interval (CI) limits or standard errors. Continuous outcomes were analyzed using the weighted mean difference (WMD). The precision of the effect sizes was reported as 95% CIs. A pooled estimate of the WMD was computed using the DerSimonian and Laird random effect model [19]. Cochran Q test and I^2 statistics were calculated to evaluate statistical heterogeneity and inconsistency of treatment effects, respectively, across studies. Statistical significance was set at $P < 0.10$ for the Cochran Q tests. Statistical heterogeneity across studies was assessed using the I^2 test, which quantifies the proportion of the total outcome variability across studies.

3. Results

3.1. Trial characteristics

Fig. 1 illustrates the flowchart for the screening and selection of trials. The initial search yielded 645 citations, of which 601 were ineligible based on the criteria used for screening titles and abstracts. Therefore, full text of 44 studies was retrieved. However, 29 have investigated treatment with other treatments such as exercising and yoga, 5 were related to acupuncture and AIA but not