Article

Acupuncture for Aromatase Inhibitor–Induced Arthralgia: A Systematic Review

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Abstract

Background. Aromatase inhibitors (AIs) are commonly used as adjunctive hormone treatment for early breast cancer patients. The major side effect of AIs is arthralgia, which affects adherence. Previous reviews suggested that acupuncture is effective in the management of cancer-related pain. The aim of this review is to evaluate the effects of acupuncture on arthralgia caused by AIs. *Methods*. This article examined randomized controlled trials (RCTs) measuring the effects of acupuncture on joint symptoms caused by AIs within 8 medical databases till May 2014. The quality of the articles was evaluated according to the Cochrane risk of bias (ROB) tool. *Results*. Four RCTs were identified in medical journals. Two studies were conducted with manual acupuncture and 2 studies were electroacupuncture. The range of sample size was between 32 and 67. One RCT showed significant improvement in the acupuncture group compared with the sham control group and another RCT showed a statistical difference between the electroacupuncture and waitlist group. The other 2 studies showed no statistical differences between control and acupuncture groups. Two studies conducted blood analysis to elucidate the mechanism of efficacy of acupuncture for arthralgia. The 2 positive studies had a lower ROB and 2 studies had a high ROB. *Conclusions*. The systematic review suggests that acupuncture has potential benefits to improve arthralgia caused by AIs. However, further trials of adequate sample size, appropriate control group, and longer follow-up are necessary to investigate the efficacy of acupuncture in AI-induced arthralgia.

Keywords

acupuncture, breast cancer, aromatase inhibitors, arthralgia, joint pain, pain management

Introduction

Breast cancer is the most commonly diagnosed female cancer in Australia and the United States.[1,2] Elevated estrogen levels increase breast cancer risk.[3-5] Tamoxifen and aromatase inhibitor (AI) are adjuvant hormone treatments commonly prescribed for hormone receptor–positive women with early breast cancer. Recently, accumulated evidences support that AIs have superior benefits to tamoxifen in survival and rate of recurrence or distant metastases.[6,7] This led the American Society of Clinical Oncology to recommend AIs for postmenopausal breast cancer patients who were hormone receptor–positive.[8,9] Currently, there are 3 third-generation AIs: 2 nonsteroidal AIs (anastrozole and letrozole) and 1 irreversible steroidal AI (exemestane).[10] Studies reported that they have similar effectiveness and toxicity profiles.[11,12]

The side effects associated with AIs are menopausal symptoms such as hot flashes and vaginal dryness, sexual dysfunction, musculoskeletal symptoms, osteopenia/osteoporosis, bone fracture, fatigue, mood disturbance, nausea, and vomiting.[6,11-13] Joint pain and stiffness are regarded as the most severe side effects reported by 35% to 81% of AI users.[6,14-18] AI-induced arthralgia affects medication adherence and leads to premature discontinuation of AIs.[17-19] Patients use doctor-prescribed medications, complementary medicine and alternative therapies to control AI-induced arthralgia. As adjunctive medications, anti-inflammatories, codeine, morphine, paracetamol, and chondroitin are used.[16] In the case that joint

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symptoms are not controlled, switching to tamoxifen can be considered.[20,21] To date, however, there is limited evidence to control AI-induced arthralgia.

Recently, acupuncture has become widely used for pain management in cancer supportive and palliative care.[22-27] Moreover, literature reviews suggested that acupuncture has the potential to manage the symptoms of pain, nausea and vomiting, hot flashes, radiation-induced xerostomia, chemotherapy-induced neutropenia, fatigue, and chemotherapy-induced peripheral neuropathy.[28-33] Previous systematic reviews evaluating acupuncture for cancer-related pain have concluded that acupuncture may have a positive impact on patients with pain but at this time there is insufficient evidence to support this hypothesis.[22-27] The aim of this systematic review is to evaluate the current published studies reporting the effect of acupuncture on AI-induced arthralgia.

Methods

Search Strategy

Electronic literature searches were performed using PubMed, Medline, ProQuest, ScienceDirect, Cochrane Library, EMBASE, CINAHL, and PsycInfo from their inceptions to May 2014. The search was conducted using the following combination of terms: "acupuncture," OR "electroacupuncture," AND "breast cancer," AND "aromatase," AND "joint pain," OR "stiffness," OR "arthralgia," OR "musculoskeletal symptom." In the initial stage, the reviewer screened the titles and abstracts of all the available publications in order to determine eligibility. Two reviewers (KB and BO) independently applied the inclusion criteria, screening full texts. The 2 reviewers compared results and resolved any discrepancies by agreement.

Eligibility Criteria

Randomized controlled trials (RCTs) that investigated the effect of acupuncture on AI-induced joint symptoms as a primary outcome were eligible. The systematic review included full-text articles published in English.

Quality Assessment Criteria

The quality of the studies were assessed using the Cochrane risk of bias (ROB) tool (version 5.1.0).[34] The use of a ROB tool has been encouraged and advocated to reviewers conducting systematic reviews. The Cochrane ROB tool involves assessment of the ROB arising from evidence-based methodological features.[35] There are 7 domains included in this tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.[34]

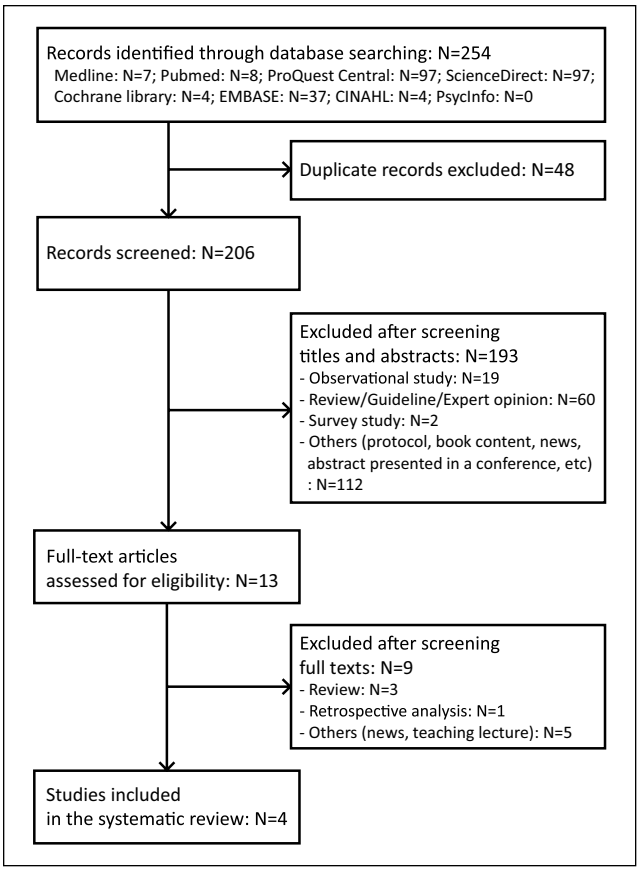

Figure 1. Flowchart for selection of studies.

The review authors judge the ROB of each domain by indicating high risk, low risk, or unclear risk. Two reviewers (KB and BO) assessed ROB independently and discussed to arrive at a consensus. Figures were generated to display the ROB judgments graphically across the included studies.

Results

Study Selection

Figure 1 shows the flow of the information of the review. The initial search yielded 254 bibliographic records from the electronic databases. Duplicates (n = 48) and 193 articles were excluded after screening titles and abstracts. On closer inspection of the full texts, only 4 studies met the eligibility criteria and were included in the review.

Results of the Studies

For clarity, the order of 4 RCTs in Table 1 is arranged from positive studies to equivocal studies.

One study reported that there was a significant difference between the electroacupuncture (EA) and waitlist control (WLC) groups but that there was no difference between EA and sham electroacupuncture (SEA) groups.[36] Another

Table 1. The Characteristics of the Studies Involving the Use of Acupuncture for Aromatase Inhibitor–Induced Joint Pain and Stiffness.

Year/ Reference	Study Design	Sample Size	Dropout Rate (%)	Intervention	Acupuncture Treatment	Control Group	Outcome Measurement Tool	Adverse Effect	Conclusion
2014/Mao et al[36]	Three-arm RCT	Total N = 67 EA (n = 19) SEA (n = 19) WLC (n = 21)	5.3 (EA, 4.5; SEA, 9.1; WLC, 4.3)	EA Electrical stimulation 2 Hz 10 sessions 2×/2 weeks 1×/6 weeks	Standard acupuncture points + most painful joint specific points	WLC SEA: Streitberger sham needles, non-acupoints	(1) Pain: BPI, WOMAC (2) Functional ability: DASH, PPT (3) Global Impression of Change	Pain at the needling site (n = 8)	(1) EA > WLC: significantly effective (2) SEA > WLC: significantly effective (3) EA vs SEA: nonsignificant
2010/Crew et al[37]	Two-arm RCT	Total N = 43 MA (n = 20) SA (n = 18)	11.6 (MA, 13.0; SA, 10.0)	MA 12 sessions 2×/6 weeks	Standard acupuncture points + most painful joint (up to 3) specific points, + auricular acupuncture	SA: Superficial needle insertion, non-acupoints	(1) Pain: BPI-SF, WOMAC, M-SACRAH	Moderate pain (n=3)	(1) MA > SA: significantly effective
2013/Oh et al[38]	Two-arm RCT	Total N = 32 EA (n = 14) SEA (n = 15)	9.4 (N/A)	EA Electrical stimulation 0.5-0.7 ms, 2-10 Hz 12 sessions 2×/6 weeks	Standard acupuncture points	SEA: Streitberger sham needles, real acupoints	(1) Pain: BPI-SF, WOMAC (2) QOL: FACT-G (3) Functional ability: Grip test (4) Inflammation biomarker: CRP, ESR (5) Perceived benefits and acceptability of acupuncture	Minor bruising on acupuncture points (n = 5)	(1) EA vs SEA: nonsignificant (2) Positive trends were observed
2013/Bao et al[39]	Two-arm RCT	Total N = 51 MA (n = 23) SA (n = 24)	7.8 (MA, 8.0; SA, 7.7)	MA 8 sessions 1×/8 weeks	Standard acupuncture points	SA: Sham needles with the Park holding device, sham acupoints (irrelevant points)	(1) Functional ability: HAQ-DI (2) Pain: VAS (3) Hormone: serum estradiol (4) Opioid neuropeptide: serum β-endorphin (5) Inflammation biomarker: serum cytokines	N/R	(1) MA vs SA: nonsignificant (2) Positive trends were observed

Abbreviations: BPI, Brief Pain Inventory; BPI-SF, the Brief Pain Inventory–Short Form; CRP, C reactive protein; DASH, Quick Disability of Arm, Shoulder, Hand; EA, electroacupuncture; ESR, erythrocyte sedimentation rate; FACT-G, Functional Assessment of Cancer Therapy–General; HAQ-DI, Health Assessment Questionnaire Disability Index; MA, manual acupuncture; M-SACRAH, Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands; N/A, not available; N/R, not reported; PPT, Physical Performance Test; QOL, quality of life; RCT, randomized controlled trial; SA, sham acupuncture; SEA, sham electroacupuncture; VAS, pain visual analog scale; WLC, waitlist control, "usual care" group; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

study reported a significant difference in joint pain between manual acupuncture (MA) and sham acupuncture (SA) control groups.[37] The 2 other studies reported that there was no significant difference between acupuncture and control groups.[38,39] The studies were conducted in the United States (n = 3) and Australia (n = 1). Three studies had 2 arms (intervention group vs sham group) while 1 study had 3 arms (intervention group vs sham group vs waitlist group). The range of sample size was between 32 and 67. The inclusion criteria of participants of four studies were comparable. To screen the eligibility criteria, 3 studies used the patients-reported outcome (PRO) instrument[36-38] while 1 study recruited based on the physician-documented AI-associated musculoskeletal symptoms.[39] The dropout rate of the 4 studies was less than 12%.[36-39] No severe adverse effects were reported apart from minor bruising and pain at the needling site.[36-39]

Intervention

There were differences in the treatment intervention. The number of treatment intervention sessions was between 8 and 12. The treatments were delivered over 6 to 8 weeks; 3 studies assessed outcomes at week 12 for durability of response.[36,37,39] Two studies used standard acupuncture points[38,39] while the other 2 studies added individualized acupuncture points based on patients' joint symptoms in addition to standard acupuncture points.[36,37] One study used both full-body acupuncture points and auricular acupuncture points.[37] In 2 studies, low-frequency electrical stimulation was provided by an electroacupuncture unit or a transcutaneous electrical nerve stimulation unit.[36,38] During the intervention sessions, all participants of the 4 RCTs were allowed to take their usual medications.

Statistical Analysis

Two studies[36,39] used intention-to-treat analysis; one[37] used per-protocol analysis, and the other study did not report on the treatment of missing data.[38] Three of the 4 studies had a sample size sufficient to have 80% power to detect clinically relevant difference when designing the study.[36,37,39] However, when calculating the sample size, minimally clinically important differences of corresponding outcome measures were derived from preliminary data of various symptoms such as rheumatoid arthritis or diabetic neuropathy, not AI-induced arthralgia.[36,37,39-42]

Outcome Measurements

Various outcome measurements, none of which had been primarily designed for AI-induced joint symptoms, were used in 4 studies. The primary outcome data were collected with PRO tools. While 3 RCTs used common outcome measures (Brief Pain Inventory–Short Form [BPI-SF], Brief Pain Inventory, and Western Ontario McMaster Universities Osteoarthritis Index [WOMAC]),[36-38] 1 RCT used the Health Assessment Questionnaire Disability Index (HAQ-DI) and the pain visual analog scale (VAS).[39] In addition, studies collected secondary outcomes with the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH) to evaluate pain,[37] the Quick Disability of Arm, Shoulder, Hand (DASH), the Physical Performance Test (PPT) for functional ability,[36] and the grip test for hand strength.[38] One study used the Functional Assessment of Cancer Therapy–General (FACT-G) to evaluate quality of life (QOL).[38] To define clinical importance from the patient's perspective, 2 trials assessed Global Impression of Change[36] and perceived benefits and acceptability of acupuncture.[38]

Blood analysis was conducted in 2 trials to elucidate the potential mechanism of efficacy of acupuncture for AI-induced arthralgia. Oh et al[38] measured C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) and found no statistical differences. Bao et al[39] measured serum estradiol, β-endorphin, and pro-inflammatory cytokines (interferon-γ, interleukin-1 [IL-1], IL-6, IL-8, IL-10, IL-12, IL-17, and tumor necrosis factor-α) concentrations at both baseline and week 8; 25-hydroxy vitamin D level at baseline.[39] Blood analysis found that serum estradiol in both groups remained undetectable at baseline and week 8. All of cytokines and β-endorphin had no difference at baseline and week 8, but IL-17 was significantly reduced in both groups and IL-12 was increased only in SA group.

Assessment of Risk of Bias

Adhering to the Cochrane ROB tool, 2 studies were adequately powered with low ROB.[36,37] The study by Oh et al[38] had a high risk of reporting bias due to nonpublication of some results (Table 2). The study by Bao et al[39] had an unclear risk of selection bias and a high risk of other bias. In this study, the baseline HAQ-DI score was significantly higher in the MA than the SA group.[39]

Discussion

This systematic review found that 1 RCT reported significantly improved arthralgia compared with the control group.[37] The 3-arm RCT demonstrated that EA significantly improved AI-induced joint pain compared with the WLC, but not the SEA.[36] Two RCTs failed to find a significant difference between real acupuncture intervention and SA groups, but it was found that joint pain and functional ability[38,39] improved in both groups.

The fact that the sham control group shows an improvement comparable to the real acupuncture group highlights an issue with the use of sham needles in study design. Since

Table 2. Assessment of Risk of Bias Based on the Cochrane Risk of Bias Tool.[a]

Year/Reference	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
2014/Mao et al[36]	+	+	+	+	+	+	+
2010/Crew et al[37]	+	+	+	+	+	+	+
2013/Oh et al[38]	+	+	+	+	+	−	+
2013/Bao et al[39]	+	?	+	+	+	+	−

[a] + low risk of bias; ? unclear risk of bias; − high risk of bias.

the introduction of SA in acupuncture RCTs, there has been heated debate among academic researchers as to whether SA is an inert control procedure or an active intervention.[43-45] To overcome this unresolved acupuncture RCT design, certain complementary and alternative medicine researcher groups suggested a 3-arm design (real acupuncture vs SA vs WLC)[46] similar to the study of Mao et al.[36] Also, including a WLC group is important in order to account for natural history that symptoms may improve over time from the initiation of AIs. Moreover, other control group settings such as standard medical care, exercise, and massage are necessary in order to compare the efficacy between acupuncture and conventional treatments. However, with the 3-arm design, there is more onus on the interpretation of data and sample size.[47]

Furthermore, acupuncture RCTs included in this review had discrepancies in the selection of acupuncture points, frequency of treatment, period of intervention, and treatment method among the 4 studies. Thus, when designing future studies, the researcher should consider these factors in planning effective acupuncture intervention to treat symptoms induced by AI as well as considering the complexity of sham acupuncture.

Moreover, 2 studies measured biochemical parameters to elucidate the mechanism of acupuncture on AI-induced arthralgia.[38,39] Oh et al[38] measured CRP and ESR but failed to demonstrate a significant change while a previous study reported the elevation of ESR and CRP after 6 months of AI initiation.[48] Similar to the rheumatoid arthritis[49] study suggesting that joint inflammation is associated with number of cytokines (tumor necrosis factor-α, IL-1, IL-4, IL-6, IL-10), the study by Bao et al[39] showed that the reduction of IL-17 is modestly associated with improvement in HAQ-DI and VAS scores. Therefore, further rigorous studies are required to elucidate the mechanism of acupuncture on AI-induced arthralgia taking account of aforementioned complexities.

Generally, RCTs are considered as high-quality evidence, but RCTs with a high ROB can produce misleading results.[50] Thus, the methodological quality of articles included in the review was assessed with the Cochrane ROB tool as developed by the Cochrane Collaboration.[34] A major issue with design of acupuncture RCTs is the blinding of the person administering the intervention and SA. Unlike pharmaceutical drug trials, most lifestyle intervention trials, including acupuncture, face issues with the blinding of person administering the intervention. In the 4 acupuncture trials included in this review, acupuncturists were not blinded for the allocation of patients. This factor can be a source of bias in acupuncture RCTs. However, in this review, we did not consider it as a major bias as suggested by the Cochrane Collaboration. It stated that the review authors can make a judgment of low ROB, when the outcome is not likely to be influenced by no blinding or incomplete blinding,[34] although the Consolidated Standards of Reporting Trials (CONSORT) statement suggested reporting the blinding status of person administering the intervention.[51]

A major limitation of this review is that it included studies with small sample sizes, short-term follow-up, and a limited number of studies. Across the studies, sample sizes were not sufficient to determine the effect of acupuncture on AI-induced arthralgia. In addition, most studies calculated sample size based on non-AI-related study data. Three studies assessed outcomes at week 12, after 6 to 8 weeks of intervention.[36,37,39] About 72% of patients reporting AI-induced arthralgia perceived the onset of joint symptoms within the first 3 months from the initiation of AIs[18] and the American Society of Clinical Oncology guidelines recommended a minimum of 5 years of adjuvant AI treatments.[8,9] Therefore, current short-term studies have an important limitation of evaluating long-term effects of acupuncture for lengthy joint symptoms caused by AIs.

There is, moreover, a potential publication selection bias, as we only examined studies published in English. Despite these limitations, the significance of this study is the systematic review aimed at determining the effects of acupuncture on AI-induced arthralgia.

Conclusions

Aromatase inhibitor–induced arthralgia is a major adverse effect experienced by breast cancer patients when they are taking AIs to prevent the recurrence or the development of contralateral breast cancer and to prolong survival. This review suggests that acupuncture has a potential to manage

AI-induced arthralgia although evidence is inconclusive. Thus, future studies of larger sample size, longer follow-up, and appropriate control settings are required to provide scientific evidence to patients, acupuncture practitioners, and oncology clinicians.

Authors' Note

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Declaration of Conflicting Interests

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