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Original Article

How does pretreatment expectancy influence pain outcomes with electroacupuncture and battlefield acupuncture in cancer survivors? Pretreatment expectancy and pain reduction by acupuncture

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ABSTRACT

Background: Outcome expectancy is an important component of non-specific effect that may play an important role in pain research and clinical care. We sought to evaluate whether pretreatment expectancy predicts pain reduction in cancer survivors receiving electroacupuncture (EA) or battlefield acupuncture (BFA).

Methods: We analyzed data from a randomized clinical trial that compared EA and BFA versus wait list control (WLC) for chronic musculoskeletal pain in cancer survivors. Expectancy was measured by the Acupuncture Expectancy Scale (AES) at baseline. Pain severity was assessed using the Brief Pain Inventory (BPI) at baseline and week 12. For each treatment arm, multivariable regression models were used to evaluate the association between pretreatment expectancy and week 12 pain severity, controlling for baseline pain severity, age, sex, race, and education.

Results: Among 360 participants enrolled, the mean age was 62.1 years (SD 12.7), with 251 (69.7 %) women and 88 (24.4 %) non-white survivors. Pretreatment expectancy was similar for all groups at baseline (EA: 13.9 ± 3.6; BFA: 13.2 ± 3.7, WLC:12.8 ± 3.3, $p = 0.14$). Greater pretreatment expectancy was not significantly associated with greater pain reduction in any group, after adjusting for co-variates (EA: Coef. = -0.05, 95 % CI = -0.14 – 0.04, $p = 0.28$; BFA: Coef. = -0.07, 95 % CI = -0.16 – 0.02, $p = 0.15$; WLC: Coef. = -0.09, 95 % CI = -0.25 – 0.06, $p = 0.23$).

Conclusions: Pretreatment expectancy did not predict pain reduction for either EA or BFA in cancer survivors. Our study contributes to the interpretation of analgesic effects of EA or BFA, beyond the notion of a mere 'placebo effect'.

1. Introduction

Chronic pain is one of the most common and disruptive symptoms experienced by cancer patients and survivors.[1,2] Pharmacological analgesics provide inadequate relief for many patients.[3-6] The American Society of Clinical Oncology Guideline recommends acupuncture as a non-pharmacological option, especially for aromatase inhibitor (AI)–related joint pain.[7] Evidence shows that acupuncture delivers clinically meaningful and durable pain reductions with minimal side effects when compared with usual care or analgesics in various cancer populations.[8,9] However, the non-specific effects, often labeled as "placebo effect" of acupuncture are not fully understood,[10-12] confounding the interpretation of acupuncture's specific effects, such as needling effects from acupoints, needling depth, and manipulations, and limiting confidence in clinical applications.[13]

Patients' expectancy around the effectiveness of pain therapies is a key component of nonspecific effects,[14,15] accounting for up to 69.8 % of pain rating variance in some acupuncture studies.[16] Acupuncture has many different forms of needle stimulation in clinical practice and research such as manual acupuncture, use of electro-stimulation of needles known as electroacupuncture, use of sham needles in sham acupuncture, and applying needles to ears known as auricular acupuncture. The effect of different needling stimulation may be influenced by pretreatment expectancy. For example, in a small study in breast cancer survivors with AI-associated arthralgia ($N = 67$) pretreatment expectancy predicted treatment response in sham acupuncture (SA) participants,

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but not in those receiving electroacupuncture (EA) ,[17] which raises to question whether different needle stimulations may respond differently to pretreatment expectancy.

Building on our prior observation, we aimed to evaluate the association between pretreatment expectancy and pain reduction due to EA or battlefield acupuncture (BFA) for chronic musculoskeletal pain.[18] We hypothesized that EA would produce clinically important pain reduction regardless of pretreatment expectancy, whereas BFA's pain reduction will be more dependent on pretreatment expectancy. Understanding the nonspecific effects, such as expectancy, on pain within the context of acupuncture trials may serve to inform not only trial design but also the clinical application of acupuncture, considering the psychological attributes of patients.

2. Methods

2.1. Study design, participants, and procedure

This study evaluates a secondary objective of the PEACE trial. The design and primary endpoint results of the PEACE trial have been published.[18,19] The trial was a 3-arm, single-center, multisite randomized clinical trial (RCT) that investigated EA and BFA versus wait-list control (WLC) for chronic musculoskeletal pain in cancer survivors (ClinicalTrials.gov Identifier: NCT02979574). Interventions were delivered over 10 weeks. Outcomes were assessed at baseline and week 12. Recruitment was conducted from March 2017 to October 2019. The institutional review board at Memorial Sloan Kettering Cancer Center approved this study (IRB Number: 16-1579).

English-speaking adult survivors diagnosed with any type of cancer were considered eligible if they had no current evidence of disease, completed active treatment (surgery, chemotherapy, and/or radiotherapy) at least 1 month before study initiation, experienced musculoskeletal pain for at least 3 months and had at least 15 days with pain in the preceding 30 days, and scored at least 4 in their worst pain on a 0–10 numerical rating scale in the past week. Survivors with non-musculoskeletal pain syndromes (e.g., headache and visceral abdominal pain) as co-morbid conditions were also eligible if they reported musculoskeletal pain as the primary source of pain. Survivors were not eligible if they had inflammatory arthritis requiring disease-modifying drugs, phantom limb pain, a pending pain-related Veteran Administration, social security, or worker's compensation disability claim by self-report, or an implanted electronically charged medical device.

After initial screening, trained research stuff met with potential participants to confirm all inclusion/exclusion criteria were met. Eligible survivors provided informed consent and completed baseline assessments including demographic and clinical characteristics, and treatment expectancy. Survivors were asked their expectancy for EA and BFA separately in all three groups. Then survivors were randomly assigned with a 2:2:1 ratio to three groups, using permuted block randomization with a secure computer system and stratified by accrual site and baseline opioid use.

2.2. Interventions

EA is a common acupuncture procedure where pairs of sterile, single-use, metallic needles are attached to a device that delivers a gentle electric current.[20] In our trial, licensed acupuncturists used a semifixed manualized acupuncture protocol with at least 4 local points around the body area with the most pain plus at least 4 additional points at the distant area to address the comorbid symptoms, totaling 10–20 acupoints. Acupuncturists manipulated the needles (30 mm or 40 mm and 0.16 mm - 0.25 mm gauge, Seirin-America Inc., Weymouth, MA) to achieve the "De Qi" sensation (including soreness, numbness, or distension), then electrically stimulated four local points for 30 min at 2 Hz using an A3922 E-STIM II device (Tens Plus Industrial Company). Participants received a total of 10 treatments over 10 weeks.

BFA was delivered by the same acupuncturists using a fixed protocol of 5 acupoints in each ear, to be stimulated in the following sequence: Cingulate Gyrus, Thalamus, Omega 2, Point Zero, and Shen Men. After placing the Aiguille Semi-Permanente (ASP) needles (2.5 mm, Lhasa OMS, Weymouth, MA) in the Cingulate Gyrus on one ear, acupuncturists instructed participants to walk for 1 min. If they rated their pain severity greater than 1 (using a 1 to 10 scale) after walking, and they wanted to continue, acupuncturists placed the needle in the same point on the other ear. The process continued in this fashion through the sequence as appropriate. The session was stopped if: 1) pain severity decreased to 1 or lower; 2) survivors asked to stop the treatment process due to discomfort; or 3) significant vasovagal reaction was observed. The total duration for each clinic treatment was about 10 to 20 min. Survivors were instructed to remove these needles by themselves after 3 to 4 days. Survivors received treatments once a week for 10 weeks.

Survivors in the WLC continued to receive their standard medical care and pain management prescribed by their health care providers, including analgesic medications. After the 12 weeks follow up, survivors had the option of receiving up to 10 treatments of their choice of EA or BFA.

2.3. Expectancy measurement

Participants' expectancy for EA and BFA was measured by the Acupuncture Expectancy Scale (AES) at baseline. AES has demonstrated good reliability (Cronbach's alpha of 0.82) and has been translated in Chinese and Korean, as well as validated in cancer survivors.[21-23] AES has 4 items evaluating survivors' expectancy for treatment regarding pain improvement, ability to cope, vitality level, and alleviation of pain. For each item, survivors rate their agreement with a relevant statement using a 5-point Likert scale (from 1 for "not at all agree" to 5 for "Completely agree"). Total scores range from 4 to 20, with higher score representing greater expectancy. For this analysis, EA patients' score was AES for EA, BFA patients' score was AES for BFA, and WLC patients' score was the mean of their AES for EA and BFA.

2.4. Primary outcome

Pain severity was measured by the Brief Pain Inventory (BPI). It is a self-reported instrument that measures both pain severity and interference. BPI was originally designed for cancer pain assessment[24,25] and has demonstrated good reliability and validity (Cronbach's alpha ranging from 0.77 to 0.91) across cultures and populations. The BPI pain severity score is based on the mean of 4 items rating the worst pain, least pain, average pain, and current pain experienced by the survivors. A 10-point scale (from 0 for no pain to 10 for pain as bad as you can imagine) is used to rate each item.

2.5. Statistical analyses

The sample size of this study was predetermined by the parent trial.[18] Patients from all three arms were included in the analysis and analyzed according to their randomized treatment arm assignment. Descriptive statistics were used to summarize BPI severity, AES score, and demographic/clinical characteristics (e.g., age, gender, and cancer type) at baseline. To evaluate the association between pretreatment expectancy and pain reduction, we first fit separate linear regression models by treatment arm with week 12 BPI score as the dependent variable and baseline AES as the independent variable, adjusting for baseline BPI score. Next, we added four covariables (age, gender, education, and race) to the first set of models to evaluate the demographic-adjusted associations between baseline AES and week 12 BPI severity. All statistical tests were two-sided, using a statistical significance threshold of $P < 0.05$ for statistical significance. Statistical analyses were conducted using R version 4.2.2 (R Core Team, 2022).

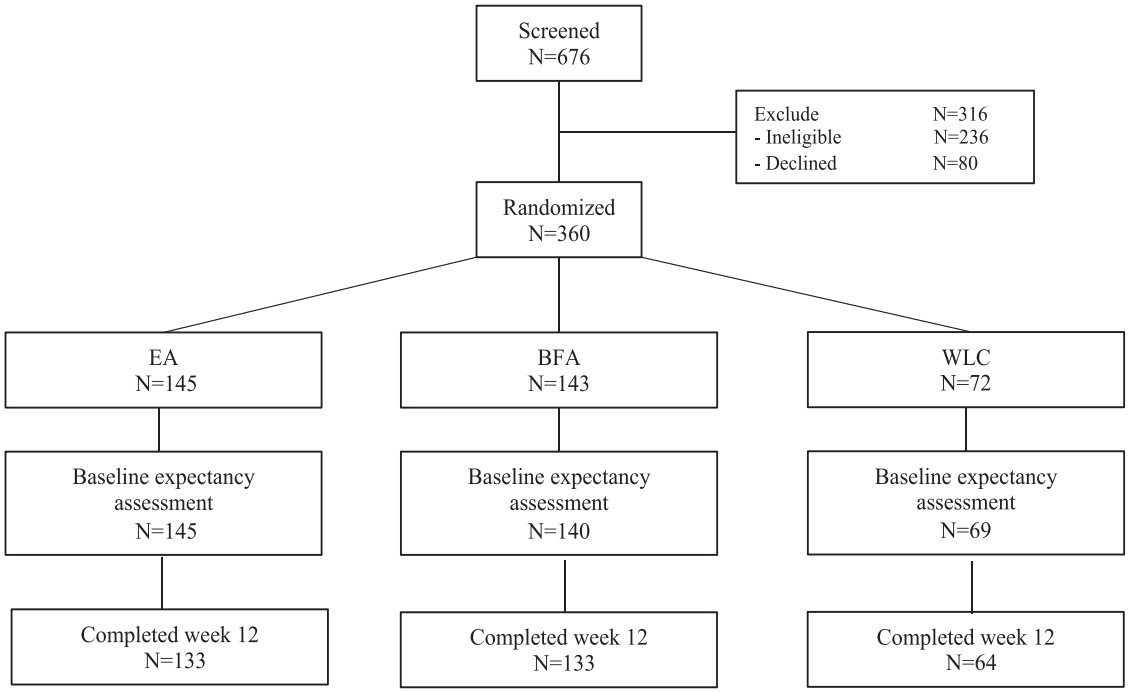

Fig. 1. Consort Diagram.

3. Results

3.1. Participant enrollment and characteristics

As previously reported,[18] we screened 676 survivors for eligibility from March 2017 to October 2019. Of these, 316 declined to participate or were ineligible. Among the 360 enrolled patients, 145 were randomly assigned to EA, 143 to BFA, and 72 to WLC. Participants in the EA and BFA groups received 10 treatments over 10 weeks. A total of 354 participants completed the AES assessment at baseline (EA: 145; BFA: 140; WLC:69), and 330 completed the BPI evaluation at week 12 (EA: 133; BFA: 133; WLC:64) (Fig. 1).

Table 1 shows participants' baseline demographic and clinical characteristics. The mean age was 62.1 years (SD 12.7). Among the participants, 251 (69.7 %) were women, 88 (24.4 %) were non-white, and 262 (73.2 %) had at least a college education. The most common cancer types were breast (45.8 %) and Lymphoma (14.2 %). The mean time since cancer diagnosis was 6.2 years (SD, 6.7) and the mean duration of pain symptoms was 5.3 years (SD, 6.5). The majority of participants (117, 32.5 %) had lower back pain. The mean pretreatment BPI score was 5.2 (SD, 1.7).

3.2. Association between expectancy and pain severity

Pretreatment expectancy scores were similar among the three groups (EA: 13.9 ± 3.6; BFA: 13.2 ± 3.7, WLC: 12.8 ± 3.3, $p = 0.14$).

There was no statistically significant association between pretreatment expectancy and pain reduction at week 12 for either EA (Coef. = −0.06, 95 % CI = −0.15 – 0.03, $p = 0.16$), BFA (Coef. = −0.03, 95 % CI = −0.12 – 0.05, $p = 0.43$), or WLC (Coef. = −0.07, 95 % CI = −0.22 – 0.08, $p = 0.34$) adjusting for baseline BPI severity.

After additionally adjusting for four demographic covariates (sex, race, age, and education), the association between pretreatment expectancy and pain reduction at week 12 remained non-significant across EA (Coef. = −0.05, 95 % CI = −0.14 – 0.04, $p = 0.28$), BFA (Coef. = −0.07, 95 % CI = −0.16 – 0.02, $p = 0.15$), and WLC (Coef. = −0.09, 95 % CI = −0.25 – 0.06, $p = 0.23$) (Fig. 2).

4. Discussion

In this randomized clinical trial, we found that pretreatment expectancy did not predict pain reduction in either EA or BFA. Our study suggests the therapeutic effects achieved by these specific forms of acupuncture are beyond the placebo effect known as expectancy.

Our study contributes to the growing understanding on the role of pretreatment expectancy and the analgesic effect of acupuncture. Our findings on EA are consistent with previous research conducted in women with aromatase inhibitors-related arthralgia and chemotherapy-induced peripheral neuropathy pain among cancer survivors,[17,26] as well as a recent study ($N = 121$) in adults with chronic low back pain.[27] However, in one study using EA to address experimentally induced pain, pretreatment expectancy did play an important role: Patients with high expectancy experienced a reduction in pain scores of approximately 2 points more, as measured by the Gracely Sensory and Affective scales, compared to those with low expectancy.[28] These divergent findings suggest that the effect of expectancy in the context of EA may have different impact for chronic and acute pain and warrant further exploration.

To our knowledge, there are no other published studies of the effect of expectancy on BFA's analgesic effect. Similar to EA, the pain reduction by BFA was not dependent on expectancy. One possible explanation is that the stimulation of the BFA through the retention of the needle in the ear for a few days provides strong and consistent stimulation, similar to the mechanism of EA. Therefore, the results were comparable between EA and BFA. However, the role of expectancy on acupuncture's analgesic effects, as indicated by current literature findings, has yielded mixed results.[29-31] This diversity in outcomes may be attributed to the heterogeneous nature of acupuncture, encompassing various styles of needle stimulation. For example, sham acupuncture used in clinical trials and Japanese acupuncture in clinical practice both use very light stimulation. Thus, in contrast to the current study, we found expectancy predicted pain reduction in sham acupuncture for aromatase inhibitor related arthralgia in our previous trial.[17]

Based on our observation, we hypothesize that the analgesic effect of EA or BFA may be mainly via bottom-up mechanism where strong and

Table 1
Demographic and clinical characteristics.

Characteristics	Total		EA		BFA		WLC	
	No.	%	No.	%	No.	%	No.	%
	360	100	145	40.3	143	39.7	72	20
Mean age (SD), y	62.1 (12.7)		61.9 (13.2)		62.6 (11.3)		61.4 (14.3)	
Gender								
Male	109	30.3	43	29.7	49	34.3	17	23.6
Female	251	69.7	102	70.3	94	65.7	55	76.4
Race								
White	272	75.6	103	71.0	109	76.2	60	83.3
Nonwhite[1]	88	24.4	42	29.0	34	23.8	12	16.7
Education								
Less than college	96	26.8	38	26.3	37	26.0	21	29.6
College grand	98	27.4	47	32.4	32	22.5	19	26.8
Graduate/Professional	164	45.8	60	41.4	73	51.4	31	43.7
Cancer type								
Breast	165	45.8	66	41.4	73	51.4	31	43.7
Lymphoma	51	14.2	22	15.2	19	13.3	10	13.9
Other[2]	144	40.0	57	43.4	51	35.3	31	42.4
Years since cancer diagnosis, mean (SD)	6.2 (6.7)		6.1 (6.5)		6.1 (6.8)		6.5 (7.0)	
Mean score (SD) of BPI	5.2 (1.7)		5.2 (1.8)		5.0 (1.7)		5.6 (1.5)	
Duration of pain, mean (SD), y	5.3 (6.5)		5.7 (6.7)		4.8 (6.3)		5.5 (6.4)	
Baseline AES, mean (SD)								
EA expectancy	13.7 (3.5)		13.9 (3.6)		13.8 (3.4)		13.0 (3.5)	
BFA expectancy	13.1 (3.7)		13.2 (3.8)		13.2 (3.7)		12.6 (3.7)	

Abbreviations: EA, electroacupuncture; BFA, battlefield acupuncture; WLC, waiting list control; AES, Acupuncture Expectancy Scale; BPI, Brief Pain Inventory.

[1] Includes Black, Asian and more than one race.

[2] Other cancer types included prostate, colorectal, melanoma, lung, and >1 cancer type.

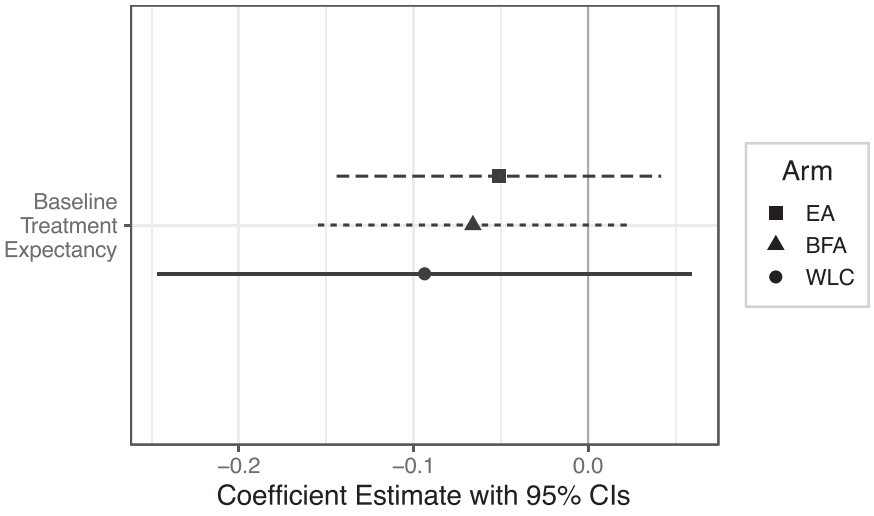

Fig. 2. Association of Pre-Treatment Expectancy on Week 12 Brief Pain Inventory (BPI) Severity by Treatment Arm, Adjusted for Baseline BPI Severity and Demographics Adjusted regression coefficients with 95 % confidence intervals for pre-treatment expectancy scores are presented from 3 treatment arm-specific linear regression models with Week 12 BPI Severity score as the outcome and pre-treatment expectancy score as the predictor of interest, controlling (adjusting) for baseline BPI Severity score and demographics (sex, race, age, and education).

consistent peripheral sensory stimulation is processed centrally to influence pain perception. According to the gate control theory proposed by Melzack and Wall,[32] activation of non-nociceptive fibers can close the gate and reduce pain perception.[33] For example, repeated stimulation of Aβ fibers excites inhibitory dorsal horn interneurons, blocking pain signal transmission from the spinal cord to higher centers in the central nervous system.[34] This mechanism contributes to the reduction of central sensitization and hyperalgesia.[35,36] Pain reduction achieved through expectancy, on the other hand, operates primarily through the top-down pathway,[37,38] involving redirecting attention away from pain and activating the opioid system.[39,40] It is possible that when acupuncture stimulation is strong enough, as in EA and BFA, the dominant analgesic effect occurs through the bottom-up pathway, unaffected by expectancy.

We also found that pretreatment expectancy did not predict pain reduction in WLC. Different from patients in the EA and BFA groups, participants in the WLC did not experience significant pain reduction (0.6 points) .[18] Additionally, the relatively small magnitude of pain reduction in the WLC group may be influenced by various factors, including the natural course of pain, regression to the mean, and other contextual effects in addition to expectancy. Therefore, the impact of expectancy on pain reduction in the WLC group might be weak.

Our study has several limitations. First, the pretreatment expectancy was not completed by every participant (98 %), which may be due to the

response bias. Second, there was an 8 % dropout rate in our study. However, pretreatment expectancy scores were similar between participants who dropped out of the trial and those who completed the week 12 assessment (13.5 ± 3.7 vs. 13.7 ± 3.4, $p = 0.8$). Nonetheless, the dropout rate in this study is considered low for an RCT.[41] Third, we only used EA and BFA with strong stimulation, so findings may not be over generalized to other modalities (e.g., manual, laser, Japanese acupuncture). Further, participants were not blinded to either EA or BFA. Additionally, our study did not incorporate a sham control; therefore, we don't know if the results can be extended to trials with treatment blinding or sham controls. Finally, as our study was conducted in the cancer population, the results may not be directly applied to the general population.

This is the largest RCT to evaluate the association between expectancy and chronic pain reduction in diverse cancer survivors receiving BFA and EA. Our findings support the therapeutic value of acupuncture for pain, going beyond the notion of a mere "placebo effect" typically attributed to expectancy.

Declaration of competing interest

The authors declare the following financial relationships: JJM reports grants from Tibet Cheezheng Tibetan Medicine Co Ltd and Zhongke Health International LLC outside the submitted work. Other authors declare no conflicts of interest.

CRediT authorship contribution statement

Xiaotong Li: Conceptualization, Writing – original draft, Methodology. **Raymond E. Baser:** Methodology, Writing – review & editing. **Karolina Bryl:** Writing – review & editing. **Lindsay Amann:** Writing – review & editing. **Susan Chimonas:** Writing – review & editing. **Jun J. Mao:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration

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Ethical statement: This research was reviewed and approved by the institutional review board at Memorial Sloan Kettering Cancer Center (IRB Number: 16-1579). Informed consent was obtained from all participants.

Data availability: The data associated with this article can be requested to the corresponding author.

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