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Impact of Baseline Expectancy on Outcome Prediction of Real and Sham Acupuncture for Persistent Chemotherapy-Induced Peripheral Neuropathy Pain in Solid Tumor Survivors: A Secondary Analysis of a Randomized Clinical Trial

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) pain significantly worsens cancer survivors' quality of life. Expectancy may play an important role in acupuncture response. We sought to explore whether expectancy predicts pain outcome in real acupuncture (RA) and sham acupuncture (SA) in cancer survivors. **Methods:** We analyzed data from a randomized clinical trial that evaluated the effect of RA on CIPN symptoms compared to SA and wait list control (WLC) in 75 cancer survivors. This secondary analysis was limited to CIPN pain measured by the Numeric Rating Scale (NRS), graded from 0 to 10. Interventions were delivered over 8 weeks. SA was implemented using a combination of non-acupuncture points and a non-insertion procedure. Patient expectancy was measured by the Acupuncture Expectancy Scale (AES) 3 times during the study. We used a linear regression model to evaluate if the NRS score was associated with the baseline AES score at the end of treatment (week 8), adjusting for baseline NRS score. **Results:** AES was similar among 3 groups at baseline (RA: 11.8 ± 2.7; SA: 12.1 ± 3.8.; WLC: 14.6 ± 4.2; $P = .062$). Baseline AES was not found to be significantly associated with the week 8 NRS score among patients in all RA, SA, and WLC groups (all $P > .05$). However, we found a trend that higher baseline AES predicted lower NRS score at week 8 in the SA group: a one-point higher score on baseline expectancy was associated with a 0.3-point reduction in NRS pain score ($P = .059$) at week 8. **Conclusions:** The association of baseline expectancy and acupuncture response was similar between RA and SA. However, SA seemed to rely more on expectancy than RA. Further studies with larger sample sizes are needed to confirm this finding.

Keywords

acupuncture expectancy, acupuncture, chemotherapy-induced peripheral neuropathy, sham acupuncture, pain

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) affects up to 68% of patients receiving chemotherapy and is often sensory-predominant with pain, tingling, and numbness that adversely affects the administration of planned therapies, significantly decreases patients' quality of life, and increases the annual costs of health care.[1-4] However, currently only duloxetine is recommended with moderate

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evidence and its therapeutic benefit is limited.[5,6] With an urgent need to find better solutions for patients suffering from CIPN, increasing evidence indicates the potential effectiveness of acupuncture, a non-pharmacological treatment.

Results have demonstrated the role of acupuncture in reducing CIPN symptoms, especially for pain, with minimal side effects when compared to sham acupuncture and wait list usual care groups among a variety of cancer survivors.[7,8] Although improvement has been shown in the real acupuncture group when compared to usual care, there is often a large placebo effect (synonymous with a non-specific effect) observed in the sham acupuncture control arm.[7,9,10] This non-specific effect was considered to be a psychobiological process in the whole acupuncture therapeutic context including patients' experiences, attitudes, and the preferences of patients and providers.[9,11,12] Evaluating this non-specific effect is essential to distinguish the true treatment effect of acupuncture from confounding psychological factors to advance acupuncture application for CIPN management.

Outcome expectancy—a belief that improvements will be achieved from the planned treatment—is a major component of the non-specific effect.[13,14] Most previous studies that evaluated the role of expectation of acupuncture were conducted in patients with pain.[15,16] We only identified 2 studies that evaluated the impact of expectancy in relation to acupuncture in cancer patients. One study explored the association between acupuncture expectations and bowel health among patients during radiotherapy for cancer.[17] The results showed that patients with low expectations were more likely to experience frequent stools compared to other patients. However, they combined the expectancy in both real and sham arms. Thus, we do not know if any differences existed between the 2 acupuncture groups. The other study focusing on the effect of real versus sham acupuncture on pain demonstrated that the predictive role of expectancy was only found in the sham group.[18] However, this study only included the breast cancer population. Current evidence also suggests that it is important to consider study population, expectancy measurements, acupuncture types, and health conditions when evaluating the expectancy-acupuncture response relationship.[15,16]

To the best of our knowledge, there is no evidence evaluating the role of outcome expectancy in acupuncture treatment of CIPN-induced pain management in diverse cancer populations. To further understand the potential role of expectancy on the effectiveness of acupuncture for CIPN-induced pain management, we conducted a secondary analysis to explore the association between baseline outcome expectancy and CIPN pain outcome by real and sham acupuncture treatment. We also aimed to determine if patient expectancy in each group changes over time during treatment.

Materials and Methods

Study Design

We used data from a single center, 3-arm, phase IIB, pilot RCT; we previously reported the details.[7] This parent study evaluated the effect of RA on CIPN symptoms including pain, tingling, and numbness compared to SA and WLC. All 3 CIPN symptoms were evaluated separately using the NRS. The study was conducted from July 2017 to June 2018. Interventions were delivered over 8 weeks and outcomes were assessed at baseline, and weeks 4, 8, and 12.

Participants and Procedures

Eligible participants were English-speaking adult cancer survivors experiencing moderate to severe CIPN (defined by rating of 4 or greater on the 0-10 NRS for symptoms such as numbness, tingling, or pain) who had completed neurotoxic chemotherapy at least 3 months prior to enrollment. We required participants who were taking anti-neuropathy medication to be on a stable regimen for the past 3 months. This secondary analysis was limited to the CIPN pain symptom as the main outcome since only CIPN pain showed a statistically significant reduction in the RA arm when compared to the SA arm. Thus, we only included patients who reported CIPN pain with an NRS score ≥ 1 at baseline in this study.

Patients with a pacemaker or those who had prior acupuncture treatment within the past 5 years were excluded. Enrolled participants were randomized to real acupuncture (RA), SA, or a WLC usual care group. The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center.

The treatment regimen for each group has been described in our prior publication.[7] Briefly, the RA group received ear and body acupuncture at up to 11 points with 2 points connected to electricity. The SA group received stimulation at non-acupuncture points through a non-insertion procedure. The WLC group did not undergo any acupuncture treatment.

Measurement of Expectancy

We used the Acupuncture Expectancy Scale (AES) to measure outcome expectancy at baseline, week 4, and week 8 (end of intervention). This 4-item instrument is scored by having patients self-report their expected improvement as a result of acupuncture from 1 to 5, with 1 indicating "Not at all agree" and 5 indicating "Completely agree." The total score ranges from 4 to 20, with a higher score representing greater expectancy. The AES has demonstrated reliability (Cronbach's α of .82) and validity and is also positively correlated with patient self-reported efficacy and satisfaction.[13] The AES has been validated in breast cancer survivors and was found to be sensitive to change over time in response to acupuncture treatment.[19]

Measurement of Treatment Response

The NRS is an 11-point numeric scale whose primary endpoint of the original study is the most bothersome CIPN symptom and was used to measure treatment response. It has been used extensively to measure the severity of symptoms, especially pain,[20,21] and previous studies have shown its high reliability and validity.[22,23] The NRS also has good validity and reproducibility in measuring chronic cancer pain.[24] Participants completed the NRS at baseline, week 4, and week 8. Clinical trials for multiple conditions have found that an NRS score reduction of 2 points or 30% is clinically significant.[21] In this secondary analysis, only patients with NRS pain rated 1 and above for CIPN were included. Patients self-reported their pain from 0 to 10, with 0 indicating no symptoms and 10 representing the worst symptoms imaginable. This study defines a pain responder as having at least a 30% reduction in NRS pain at week 8. Subjects who experienced less than a 30% reduction in NRS were classified as non-responders.

Statistical Analysis

The sample size of 51 participants was predetermined by the parent study. Descriptive statistics assessed expectancy and CIPN pain severity at baseline and demographic and clinical characteristics (eg, age, race, and cancer type). A linear regression model was used to evaluate if the NRS pain score was associated with the baseline AES score at the end of treatment (week 8) and in all 3 treatment groups after adjusting for baseline NRS pain score. To evaluate whether change in expectancy over time differed between responders and non-responders in each treatment group, linear mixed-effects models were developed with expectancy as the outcome; responder status and time were covariates, including the time and responder status interaction term. Time was considered as a categorical variable and was included as a random intercept term in the mixed-effects model. To evaluate whether baseline expectancy predicts treatment response, a multivariate linear regression model was built with percent reduction in NRS pain as the dependent variable. Baseline expectancy and treatment group (RA or SA) were built as independent variables, including the expectancy and treatment group interaction term. Based on these models, an expected percent NRS pain reduction based on the expectancy score for RA and SA at baseline was developed. All analyses were 2-sided with a P value of less than .05 for group comparisons and 0.10 for interaction terms indicating statistical significance. Statistical analyses were conducted using STATA (version 15.0; STATA Corporation, College Station, TX) and SAS (version 9.4; SAS Institute, Inc, Cary, NC).

Interventions

Patients randomized to either the RA or SA group received a total of 10 treatments over 8 weeks (twice weekly for 2 weeks, then weekly for 6 weeks). Licensed acupuncturists delivered both RA and SA treatments. Needles remained in place for 20 to 30 minutes for each treatment session and, in both groups, patients' eyes were covered with patches so that they could not observe the treatment procedure.

The RA regimen used a semifixed manualized acupuncture protocol.[7] It included 3 ear acupoints (Shen Men, point zero, and a third electrodermal active point)[25] and an additional 8 acupoints on the body (LI-4, PC-6, SI-3, LR-3, GB-42, ST-40, Bafeng 2, and Bafeng 3). Acupuncturists had the option of not inserting needles in the extremities that had no symptoms. The acupuncturists inserted the needles (0.16 mm × 15 mm disposable filiform acupuncture needles in the ear points; 0.25 mm × 30- or 40-mm needles of the same quality for body points) approximately 12.5 mm into the skin for the body points and 2.0 mm for the ear points. The needles were manipulated until the patient indicated experiencing *de qi* sensation (feeling of soreness, numbness, or distention). The electrical stimulation was applied on 2 body points at 2 to 5 Hz. This varies based on each patient's response and aimed at providing constant gentle simulation ranging from 0 to 40 mA.

SA was delivered using a combination of non-acupuncture points and a non-insertion procedure from a previously valid placebo acupuncture method.[26] Acupuncturists taped an empty plastic needle guiding tube on the bony area away from each of the 8 body points. Then, they applied a needle with a piece of adhesive tape to the dermal surface. They did not place any needles on the ear. The electro device was attached to the needles but was not turned on.

Patients in the WLC group continued to receive their standard medical care prescribed by their health care providers. They self-reported their pain medication use during the research period (12 weeks). After the 12-week assessments were completed, patients had the option of receiving 8 sessions of RA over 8 weeks.

Results

Patient Characteristics

As previously reported,[7] we enrolled 75 participants into the trial between July 2017 and June 2018. We excluded 24 patients from this secondary analysis because they either had no baseline pain (n = 16), no data for week 8 pain score (n = 6), no baseline expectancy score (n = 1), or no baseline pain score and no week 8 pain score (n = 1). Of the 51 remaining patients, 19 (37.3%) were assigned to RA, 17 (33.3%) to SA, and 15 (29.4%) to WLC.

Table 1. Baseline Characteristics of the Study Participants.

	All patients		RA		SA		WLC	
Variables	N	%	N	%	N	%	N	%
Age (years), median (range)	51	100	19	37	17	33	15	29
	60.5 (44.5-86.0)		61.8 (51.0-82.1)		59.9 (44.5-86.0)		59.7 (47.9-71.7)	
Gender								
Male	7	14	4	21	2	12	1	7
Female	44	86	15	79	15	88	14	93
Race*								
White	37	76	16	89	15	88	6	43
Non-white	12	24	2	11	2	12	8	57
Hispanic ethnicity	4	8	3	16	1	6	0	0
Cancer type								
Breast	31	61	10	53	10	59	11	73
Lung	1	2	0	0	0	0	1	7
Colon/rectal	9	18	4	21	4	24	1	7
Testicular	1	2	1	5	0	0	0	0
Melanoma	1	2	0	0	0	0	1	7
Head/neck	1	2	0	0	1	6	0	0
Ovarian	3	6	2	10	1	6	0	0
Endometrial	4	8	2	10	1	6	1	7
Cancer stage								
Stage I	11	22	7	37	0	0	4	27
Stage II	24	47	7	37	10	59	7	47
Stage III	14	27	5	26	6	35	3	20
Stage IV	2	4	0	0	1	6	1	7
Chemo type								
Taxane-based only	31	61	10	53	10	59	11	73
Platinum-based only	12	24	5	26	5	29	2	13
Taxane and Platinum Combined	8	16	4	21	2	12	2	13
Years since chemo, median (range)	4.4 (0.3-18.2)		4.9 (0.5-18.2)		3.9 (0.3-12.2)		4.5 (0.4-11.4)	

*$P < .05$.
Abbreviations: RA, real Acupuncture; SA, sham acupuncture; WLC, waitlist control.

Table 1 shows the baseline data for the 51 participants. The mean age was 60.5 years (44.6-86 years), 44 (86%) were women, and 37 (76%) were white. There was a racial imbalance showing a significantly greater white patient population in RA (89%) and SA (88%) compared with WLC (43%) ($P = .007$). The majority of patients had a breast cancer diagnosis, followed by colorectal cancer. The overall baseline AES was 12.8 ± 3.6 and did not differ among RA, SA, and WLC groups, although there was a trend showing that the WLC group had a higher expectancy score compared to RA and SA (RA: 11.8 ± 2.7; SA: 12.1 ± 3.8; WLC: 14.6 ± 4.2; $P = .062$).

Predicting Response by Baseline Expectancy Score

In the linear regression model with week 8 pain score as the dependent variable, baseline AES was not found to be significantly associated with week 8 pain score among patients in RA, SA, and WLC group (all $P > .05$). However, in SA, a trend where higher baseline AES correlates with a lower week 8 NRS pain score was found: a one-point higher baseline expectancy score is associated with a 0.3-point reduction in the NRS pain score at week 8 ($P = .059$).

By the end of treatment at week 8, 11 (57.9%) in RA, 8 (47.1%) in SA, and 5 (33.3%) in WLC groups were responders. We further explored the association between baseline AES and treatment responder status and did not find a significant association among all 3 groups (all $P > .05$). However, in RA, the AES was similar between responders and non-responders; in SA, the responders had two-points higher AES scores compared to non-responders; and there was a four-point difference between responders and non-responders in the WLC group (Table 2).

Change in AES Over Time

Table 2 and Figure 1 show the AES change over time by treatment groups and acupuncture response status. In the RA arm, treatment responders and non-responders were not

Table 2. Change in Acupuncture Expectancy Score over time by treatment group.

	Responder AES		Non-responder AES		
	Baseline	Week 8	Baseline	Week 8	*P*
RA	11.3 ± 2.7	10.6 ± 3.3	12.6 ± 2.6	9.3 ± 2.9	.24
SA	13.1 ± 2.7	13.2 ± 2.7	11.2 ± 4.5	10.9 ± 4.1	.76
WLC	12.0 ± 5.1	12.2 ± 3.6	15.9 ± 3.1	12.6 ± 6.8	.74

Abbreviations: AES, Acupuncture Expectancy Score; RA, real acupuncture; SA, sham acupuncture; WLC, waitlist control.

Figure 1. Change in Acupuncture Expectancy Score Over Time by Treatment Group.
Abbreviation: NRS, Numerical Rating Scale.

completely separated by baseline AES. Responders started with a lower baseline AES of 11.3 ± 2.7 than the baseline AES of 12.6 ± 2.6 for non-responders. However, during the

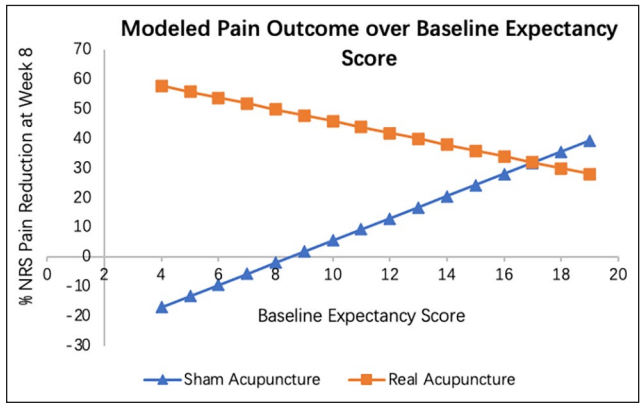

Figure 2. Modeled pain outcome over baseline expectancy score. Relationship between baseline AES and NRS percent pain reduction at Week 8.

8-week treatment period, the AES of responders remained constant over time with a mean AES of 10.6 ± 3.3 at week 8. Non-responders reported progressively lower AES with 9.3 ± 2.9 at week 8; the between group difference was not significant (P = .24). In contrast, in the SA arm, responders consistently had a higher AES than non-responders during the 8-week treatment period (baseline: responders 13.1 ± 2.7, non-responders 11.2 ± 4.5; week 8: responders 13.2 ± 2.7, non-responders 10.9 ± 4.1, P = .76). For WLC, the AES for responders remained constant, but the AES for non-responders decreased during the 8-week period (baseline: responders 12.0 ± 5.1, non-responders 15.9 ± 3.1; week 8: responders 12.2 ± 3.6, non-responders 12.6 ± 6.8, P = .74).

Figure 2 models the relationship between percent NRS reduction at the end of treatment and baseline AES for the RA and SA groups. At low AES scores, RA was found to have consistently better treatment effect than SA, whereas, with high AES scores the effect of SA increased and even surpassed the treatment effect of RA.

Discussion

There is growing interest in evaluating the impact of outcome expectancy on acupuncture response. Using data from a 3-arm RCT of cancer survivors with CIPN symptoms, our

observations suggested that RA produced clinically important pain-intensity reduction regardless of baseline outcome expectancy, whereas there was a trend that pain reduction in the SA group was more dependent on baseline outcome expectancy. This result suggests that distinct mechanisms may exist to produce the treatment effect of RA and SA. Baseline outcome expectancy may explain the apparently similar clinical effect of SA to RA.

To our knowledge, this is the first study that involved patients with CIPN-induced pain in a diverse cancer population. Previous systematic reviews evaluating the expectancy-outcome relationship in acupuncture among non-cancer population have yielded mixed results.[15,16] High heterogeneity of study populations, study methodology, and expectancy measurements have all contributed to difficulty determining the significance of these study findings. We were only able to identify one study in cancer survivors with pain; it evaluated the association between pre-treatment expectancy and aromatase inhibitor-induced joint muscle pain by electroacupuncture and SA conducted in breast cancer survivors.[18] Consistent with our study, they also did not demonstrate the predictive role of baseline expectancy on pain outcome by RA. However, instead of the trend, higher baseline expectancy predicted treatment response in SA. It is worth noting that this study had a larger sample size (n = 67) than our study and that all participants were female. Further studies with larger sample sizes in diverse cancer populations are still needed to verify these findings.

Our findings of a different trend of expectancy-outcome relationships for those in RA and those in SA suggest that the clinical effect of the 2 treatments may act through different mechanisms. Some evidence suggests that RA produces a specific physiological effect on pain, while a patient's expectation and belief for a better outcome may also modulate different components in the neural system to reduce pain.[27,28] Kong et al[27] conducted a functional magnetic resonance imaging study among healthy volunteers combining an expectancy manipulation procedure with EA and SA to explore expectancy-induced placebo/active treatment analgesia. They found that RA yielded a greater response in the pain processing regions of the brain than SA. The results indicated brain imaging evidence for variations in the different treatment mechanisms with RA and SA expectancy.

This idea is corroborated by a study that found differing neurotransmitter system activity in RA and SA in patients with fibromyalgia when evaluated using positron emission tomography with C-carfentanil, a selective agonist for μ-Opioid receptor.[29] Harris et al found that μ-opioid receptors (MORs) binding potential experienced short-term and long-term increases in multiple pain and sensory processing regions as a result of RA, whereas in SA these effects were absent or experienced small reductions, indicating a potentially different mechanism for the placebo effect experienced. For SA, high expectancy may invoke a more complicated network than low expectancy, particularly in the areas in the frontal cortex, which may lead to a similar analgesic effect as RA or opiate drugs without mutual interference.[30] In addition, it is possible that the minimal stimulation in the SA arm triggered a psychological response pathway that differed from RA, where needles penetrate the skin and achieve *de qi*, causing stronger stimulation and triggering more physiological effects. These findings provided the initial evidence that different mechanisms underlie the role of baseline outcome expectancy on treatment effect for RA and SA. This area requires further research to better understand the clinical effect of acupuncture for pain management in cancer survivors.

This study has several limitations. First, our small sample size may have led to a lack of statistically significant results, which may have occurred with a larger population size. Second, considering that our study consisted predominantly of women, it is possible that their experience of acupuncture and their expectations differ from those of men. Lastly, our study participants were predominantly white, which means our results may not represent the general population. Despite these limitations, and to the best of our knowledge, this is the first randomized clinical trial to evaluate the impact of baseline outcome expectancy on CIPN pain severity by real versus sham acupuncture.

We used a validated instrument to evaluate patients' expectancy. In addition, we measured expectancy several times during study treatment, which provided evidence for how expectancy changed over time. We found the association of expectancy and acupuncture response was similar between RA and SA. However, there was a trend of high expectancy yielding greater improved pain scores for SA only. This implies that there are potentially 2 distinct pathways leading to compatible results in CIPN pain reduction by these 2 types of acupuncture and that SA may rely more on expectancy than RA. Further studies with larger sample sizes and mechanistic exploration are needed.

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Author Contributions

Design—RW, TB; recruitment—TB; intervention—TB; data acquisition—QL; data analysis—XL, LZ, QL, RW, TB; manuscript preparation—all authors.

Availability of Data and Material

Data used in the study is available for further examination from the principal investigator (Dr. Ting Bao) on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

The study protocol has been reviewed and approved by the Institutional Review Board (IRB) of Memorial Sloan Kettering Cancer Center (MSK). All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Consent for Publication

All authors consent to publication of this manuscript.

Clinical Trial Registration

NCT03183037

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