ORIGINAL ARTICLE

Positive effects of acupressure bands combined with relaxation music/instructions on patients most at risk for chemotherapy-induced nausea

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Abstract

Purpose Research by our group has shown that acupressure bands are efficacious in reducing chemotherapy-induced nausea (CIN) for breast cancer patients who expect nausea, and that their effectiveness in controlling CIN can largely be accounted for by patients' expectations of efficacy, i.e., a placebo effect. The present research examined if the effectiveness of acupressure bands could be enhanced by boosting patients' expectation of the bands' efficacy.

Methods Two hundred forty-two chemotherapy-naïve patients with breast cancer who expected nausea were randomized. Arms 1 and 2 received acupressure bands, plus a relaxation MP3 and written handout that were either expectancy-enhancing (arm 1) or expectancy-neutral (arm 2). Arm 3 was the control without bands or MP3 and received standard care. All participants received guideline-specified antiemetics.

Results Peak CIN for arms 1, 2, and 3 on a 1–7 scale was 3.52, 3.55, and 3.87, respectively ($p = 0.46$). Because no differences were observed between arms 1 and 2 (primary analysis), we combined these two arms (intervention) and compared them to controls for the following analyses. A significant interaction was found between intervention/control and receiving doxorubicin-based chemotherapy (yes/no) and pre-treatment anxiety (high/low). Intervention patients receiving doxorubicin had lower peak CIN than controls (3.62 vs. 4.38; $p = 0.02$). Similarly, intervention patients with high pre-treatment anxiety had a lower peak CIN than controls (3.62 vs. 4.62; $p = 0.01$).

Conclusions In breast cancer patients undergoing chemotherapy and having high CIN expectation, acupressure bands combined with a relaxation recording were effective in reducing CIN for patients who received doxorubicin or had high anxiety.

Keywords Acupressure bands · Nausea · Anxiety · Chemotherapy · Doxorubicin · Breast cancer

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Introduction

Nausea is a prevalent side effect of chemotherapy experienced by breast cancer patients and is viewed as one of the most distressing and feared symptoms by patients, even more so than vomiting [1–3]. Because many patients do not achieve complete response with standard antiemetics, it is important to explore the additional role of non-pharmacologic interventions as an adjunct to antiemetics in the prevention and management of chemotherapy-induced nausea (CIN). Various behavioral interventions have been studied for this purpose, such as acupressure, expectation manipulation techniques, and relaxation therapy combined with guided imagery [4].

Acupressure bands apply light pressure on the skin over the P6 pressure point [5]. Although it is not clear how stimulation of the P6 pressure point reduces nausea, research done by our

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group and others provides evidence that acupressure bands are efficacious in reducing treatment-related nausea [5–10], and that acupressure bands are particularly effective for breast cancer patients who expect CIN [11]. Expectancy appears to play a dual role in the bands' effectiveness, with research also showing that their effectiveness in controlling nausea can largely be accounted for by patients' expectations of efficacy, i.e., a placebo effect [6, 12, 13]. In this regard, in addition to any intrinsic efficacy for relieving CIN they may have, the acupressure bands can be considered an inert device/remedy that facilitates a change in CIN expectancies. The interplay between patients' expectation for developing CIN and their propensity to respond favorably to an intervention designed to increase positive expectations for CIN control leads to a logical question—can the effectiveness of acupressure bands in reducing CIN be enhanced by boosting patients' expectation of the bands' efficacy? Stated otherwise, can the placebo effect be maximized and utilized for enhanced CIN control?

This question was addressed by our group in a preliminary study examining the effects of an expectancy manipulation using acupressure bands on CIN in breast cancer patients [12]. This study showed that acupressure bands provided with expectancy-enhancing material resulted in significantly improved CIN control (Cohen's $d = 0.78$) in patients with high CIN expectancies, but not for patients with low CIN expectancies. Additionally, several studies have shown that CIN expectancies are important predictors for the development/ and or severity of actual CIN above and beyond that from the emetogenicity of the chemotherapeutic agents as well as from other known predictors, such as age, gender, and anxiety [12, 14–16]. For example, Roscoe et al. [17] found that breast cancer patients, scheduled to receive doxorubicin-based chemotherapy, had a five-fold increase in severe CIN if they believed that they were "very likely" to experience severe CIN versus those who believed that they were "very unlikely" to do so.

The present study seeks to confirm and extend the findings from our preliminary study via a phase II, multicenter, three-arm, clinical trial of female breast cancer patients beginning chemotherapy and who expected to have CIN. The primary objective was to examine if acupressure bands with an expectancy-enhancing relaxation recording and a handout designed to enhance the expectation of acupressure bands' efficacy will result in greater reduction of CIN than acupressure bands with an expectancy-neutral relaxation recording and handout. Secondary objectives were to determine potential moderators of the intervention and to assess the effectiveness of bands with relaxation recording as an adjunct to standard antiemetics in controlling CIN.

Methods

Patients

Two hundred forty-two (N) participants were recruited at four cancer clinics in three Northeastern U.S. cities between January 2013 and March 2017. Eligible participants were chemotherapy-naïve female breast cancer patients at least 18 years of age, scheduled to receive their first treatment with a chemotherapy regimen containing doxorubicin, or docetaxel with carboplatin, or docetaxel with cyclophosphamide, and who expected nausea (indicated by a response of > 3 on a 5-point scale assessing expected nausea anchored at one end by 1 = "I am certain I WILL NOT have this," and at the other end by 5 = "I am certain I WILL have this"). Patients receiving concurrent radiotherapy or interferon, or with clinical evidence of lymphedema, current bowel obstruction, or symptomatic brain metastases, were excluded. The institutional review boards of the University of Rochester and each participating site approved the protocol, and participants provided written informed consent. This trial is registered with ClinicalTrials. gov, number NCT01695993.

Study design and procedures

This study was a phase II, randomized, partially blinded, placebo-controlled trial. Prior to first chemotherapy, patients were randomized to one of the three arms: (1) acupressure bands and expectancy-enhancing material (i.e., expectancy-enhancing handout concerning acupressure bands and expectancy-enhancing relaxation MP3 recording), (2) acupressure bands and expectancy-neutral material (i.e., expectancy-neutral handout concerning acupressure bands and expectancy-neutral relaxation MP3 recording), (3) control: only an expectancy-neutral handout without the mention of acupressure bands. Participants in all three groups received specified antiemetics that were in accordance with guidelines and were consistent across study sites. A table of computer-generated random numbers with a randomized block size of 3 or 6 was used to assign patients to one of three arms. Randomization was stratified by recruitment site and whether patients received doxorubicin-based chemotherapy (yes/no). Researchers and treating physicians were not blinded regarding whether patients received the acupressure bands and MP3 recording. They were blinded, however, through the judicious use of sealed envelopes and earphones as to whether those patients who received the bands were assigned to the expectancy-enhancing versus the expectancy-neutral condition.

Intervention

The complete intervention methods have been previously published [12]. Briefly, patients in arms 1 and 2 were provided two acupressure bands (Sea-Band International, England) and were instructed to place them approximately 2 in. proximal to the distal skin crease of the wrist joint. Patients in arms 1 and 2 were required to try the acupressure bands after randomization. They were, however, allowed to wear or remove the bands throughout the five intervention days at their own discretion.

The expectancy-enhancing handout provided to patients in arm 1 included the following: (1) a one-page printout of a bar graph with text that was printed on Cancer Center letterhead and signed by a medical oncologist (Fig. 1) and (2) a medical prescription, also signed by a medical oncologist, that instructed to "Wear Seabands for up to five days as needed to prevent or alleviate nausea." Patients were instructed to use the acupressure bands in addition to their antiemetic regimen and not in place of it. The printout was intended to enhance the expected acupressure band efficacy, while the prescription was designed to enhance the credibility of the acupressure bands for nausea control.

The expectancy-neutral handout given to patients in arm 2 was comprised of a thank you note for participating in the study and a non-prescription note that stated, "Use the acupressure bands in addition to your regular medication." Patients in arm 3 were given only a thank you note for participating in the study.

Both the expectancy-enhancing and expectancy-neutral relaxation music MP3 recordings were 12 min in length with a background of soothing flute music and relaxation instructions with guided imagery based on a published script [18, 19]. Compared to the neutral version, the enhancing version had additional language inserted, less than 1 min in length,
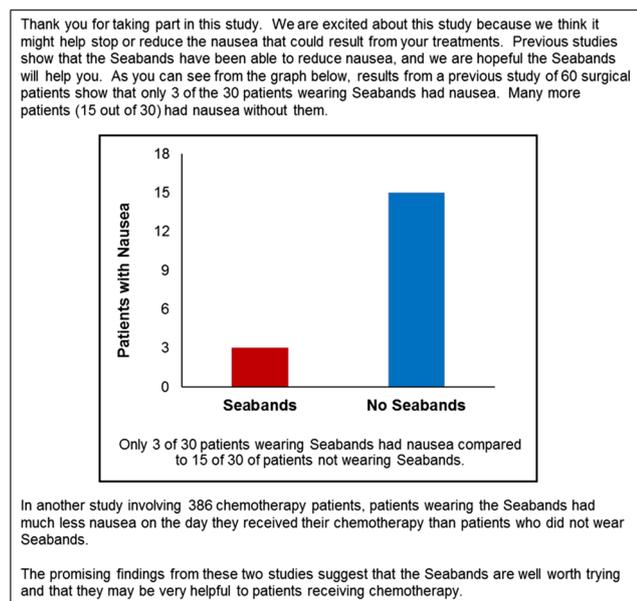

Thank you for taking part in this study. We are excited about this study because we think it might help stop or reduce the nausea that could result from your treatments. Previous studies show that the Seabands have been able to reduce nausea, and we are hopeful the Seabands will help you. As you can see from the graph below, results from a previous study of 60 surgical patients show that only 3 of the 30 patients wearing Seabands had nausea. Many more patients (15 out of 30) had nausea without them.

Only 3 of 30 patients wearing Seabands had nausea compared to 15 of 30 of patients not wearing Seabands.

In another study involving 386 chemotherapy patients, patients wearing the Seabands had much less nausea on the day they received their chemotherapy than patients who did not wear Seabands.

The promising findings from these two studies suggest that the Seabands are well worth trying and that they may be very helpful to patients receiving chemotherapy.

Fig. 1 Expectancy-enhancing handout

concerning the efficacy of the acupressure bands and control of nausea. This was intended to strengthen patients' beliefs that the acupressure bands would be effective by focusing patients' attention on how effective the acupressure bands have been in reducing or eliminating nausea for other patients. Additionally, it was suggested that since the acupressure bands were helpful to others, "we think that they will be helpful to you as well." Patients in arms 1 and 2 were required to listen to the MP3 recording once during the randomization process and told they could listen to as much or as little as they desired throughout the study period.

Measures

On enrollment, participants provided demographic and clinical information and history of nausea from various causes. "Worst level of anxiety during the last 24 h" was also assessed on an 11-point scale ranging from 0 to 10, with higher scores indicating worst anxiety. From this, a dichotomous variable of anxiety (high vs. low) was calculated (centered on the median value).

CIN was assessed by a self-report 5-day diary [20, 21] that has been used in previous large clinical trials [6, 22, 23]. Patients reported the severity of nausea four times each day (morning, afternoon, evening, and night) over a 5-day period: starting on the day of chemotherapy and on the four following days. Nausea was rated on a 7-point scale ranging from 1 (not at all nauseated) to 7 (extremely nauseated). Peak CIN was defined as the highest nausea rating across the 20 nausea assessment points from the 5-day diary. A score of ≥ 3 for peak CIN indicates moderate-severe level.

Expected worst level of CIN, assessed prior to randomization, was measured on a 5-point scale ranging from 1 (none) to 5 (intolerable). The expected band efficacy, assessed after randomization, was also measured on a 5-point scale ranging from 1 (not at all effective) to 5 (very effective). Whether patients' expectation of band efficacy changed after the informational material was provided was also assessed on a 5-point scale ranging from 1 (less likely to be effective) to 5 (more likely to be effective).

A feedback questionnaire was completed by patients at the conclusion of the study period regarding the usefulness of the acupressure bands in managing CIN. The questionnaire also assessed if the bands and relaxation music reduced apprehension and whether participants would recommend them to other patients. All questions were assessed on a 5-point scale.

Statistical analyses

In our previous study of antiemetic [22], the standard deviation for peak CIN pooled across the study arms was 1.89. Based on this number, we calculated that a sample size of 64 participants per arm would have 80% power at the 0.05 two-

sided significance level to detect a peak CIN difference of 0.82 (analysis of covariance (ANCOVA), covariate-response correlation = 0.5). Assuming an 11% dropout rate, we planned for 72 participants per arm.

The primary outcome variable was peak CIN after chemotherapy cycle 1. The analyses followed an intent-to-treat approach. Because 7% of the 242 patients did not provide CIN data after chemotherapy cycle 1, the analyses were conducted on data from 226 patients (completed cases). No data imputation was performed. Descriptive statistics were conducted. Percentages were calculated for categorical variables, and means and standard errors for continuous variables. To determine group differences, one-way analysis of variance (ANOVA) and independent t tests were used for continuous variables and chi-square tests for categorical variables.

ANCOVA was used for the primary analysis with peak CIN as the response variable, arm (1 or 2) as the fixed effect, and expected band efficacy as the covariate and was adjusted for stratifying factors (recruitment site and doxorubicin (yes/no)). We also re-ran the model after controlling for covariates that were correlated with CIN. The Spearman rank correlations were used to examine these correlations of CIN with covariates.

For the secondary analyses, the effect of acupressure bands was tested by creating two groups: bands + music (yes/no), i.e., patients who received acupressure bands with relaxation music (collapsing across arms 1 and 2) versus those who did not (control: arm 3). To determine potential moderators of the bands' effect on CIN, interactions with bands + music (yes/no) were tested. We found statistically significant interactions of bands + music (yes/no) with doxorubicin (yes/no), anxiety (high/low), and doxorubicin times anxiety (all p values $\leq$ 0.03). Further analyses (ANOVA) were stratified by these moderators, with peak CIN as the response variable and bands + music (yes/no) as the fixed effect, and were adjusted for recruitment site effect.

A two-sided p value of ≤ 0.05 was considered statistically significant in all analyses. Analyses were performed using SPSS (version 25) and SAS (version 9.4) as appropriate.

Results

Patient characteristics

Two hundred forty-two (N) patients were consented and randomized; 226 patients (93% of 242 patients) completed the intervention and provided evaluable data after the first chemotherapy on the primary outcome of peak CIN (Fig. 2). Over the 5-day period, the average number of hours the patients used the acupressure bands was 56 (0–120) h and the average number of times the patients listened to the relaxation music was 5 (0–31); there were no significant differences between arms 1 and 2. No serious study-related adverse events were reported. Table 1 lists the baseline characteristics by the intervention arm. Mean age was 53 years, 88% were white, 97% were non-Hispanic or Latino, 72% were married or in a committed relationship, and 67% received doxorubicin. There were no significant differences between the groups at baseline.
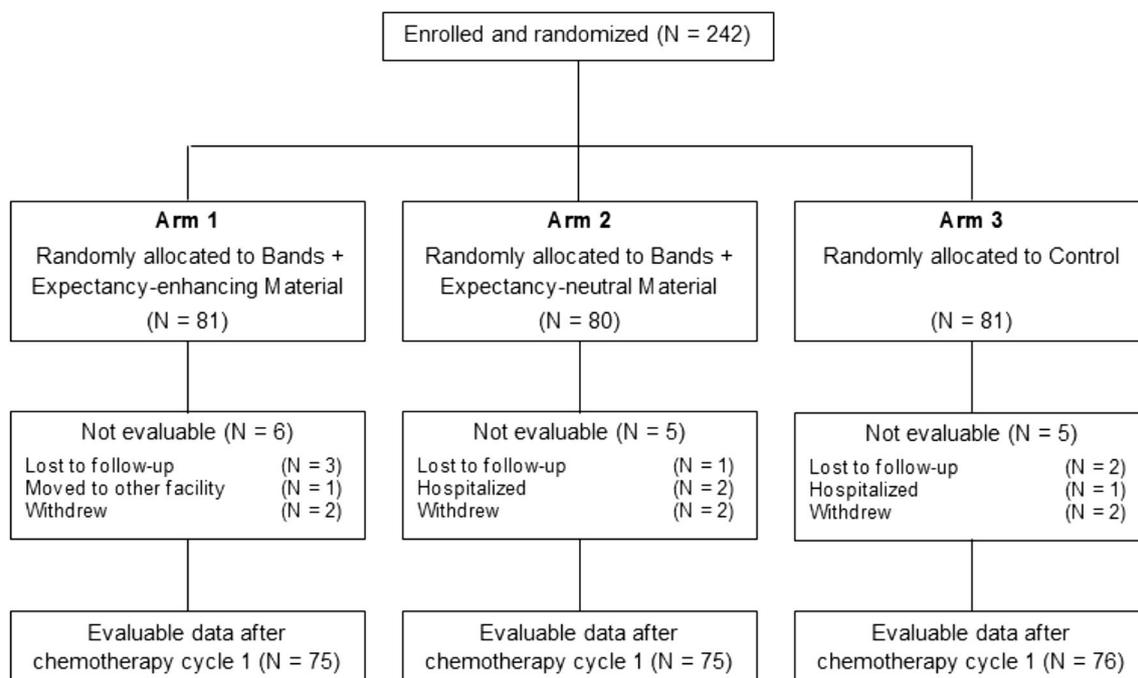

Fig. 2 CONSORT diagram

Table 1 Baseline characteristics of participants

Characteristics	Total ($N = 226$)	Arm 1[a] ($N = 75$)	Arm 2[b] ($N = 75$)	Arm 3[c] ($N = 76$)
Age				
Mean (SE)	53.0 (0.7)	52.6 (1.2)	53.2 (1.3)	53.2 (1.3)
Range	24–76	24–73	27–76	29–75
Race, n (%)				
White	199 (88.1)	66 (88.0)	66 (88.0)	67 (88.2)
Black/African American	19 (8.4)	6 (8.0)	6 (8.0)	7 (9.2)
Asian	4 (1.8)	1 (1.3)	1 (1.3)	2 (2.6)
Native American	2 (0.9)	1 (1.3)	1 (1.3)	–
Unknown	2 (0.9)	1 (1.3)	1 (1.3)	–
Ethnicity, n (%)				
Hispanic/Latino	5 (2.2)	1 (1.3)	1 (1.3)	3 (3.9)
Non-Hispanic/Latino	220 (97.3)	73 (97.3)	74 (98.7)	73 (96.1)
Unknown	1 (0.4)	1 (1.3)	–	–
Education, n (%)				
Bachelor's degree or higher	95 (42.0)	29 (38.7)	36 (48.0)	30 (39.5)
Partial college training	77 (34.1)	28 (37.3)	20 (26.7)	29 (38.2)
High school graduate or less	54 (23.9)	18 (24.0)	19 (25.3)	17 (22.4)
Marital status, n (%)				
Married/committed relationship	163 (72.1)	51 (68.0)	59 (78.7)	53 (69.7)
Divorced/widowed/separated	36 (15.9)	10 (13.3)	12 (16.0)	14 (18.4)
Single	27 (11.9)	14 (18.7)	4 (5.3)	9 (11.8)
Chemotherapy, n (%)				
Doxorubicin	151 (66.8)	50 (66.7)	50 (66.7)	51 (67.1)
Cyclophosphamide	195 (86.3)	66 (88.0)	64 (85.3)	65 (85.5)
Docetaxel	75 (33.2)	24 (32.0)	25 (33.3)	26 (34.2)
Carboplatin	30 (13.3)	8 (10.7)	11 (14.7)	11 (14.5)
Herceptin	31 (13.7)	9 (12.0)	11 (14.7)	11 (14.5)
Motion sickness, n (%)				
Yes	139 (61.5)	45 (60.0)	43 (57.3)	51 (67.1)
No	86 (38.1)	30 (40.0)	32 (42.7)	24 (31.6)
Unknown	1 (0.4)	–	–	1 (1.3)
Morning sickness during pregnancy, n (%)				
Yes	142 (62.8)	50 (66.7)	49 (65.3)	43 (56.6)
No	49 (21.7)	13 (17.3)	18 (24.0)	18 (23.7)
Not applicable	35 (15.5)	12 (16.0)	8 (10.7)	15 (19.7)
Pre-treatment anxiety, mean (SE)	4.4 (0.2)	4.6 (0.3)	4.1 (0.3)	4.5 (0.4)
Pre-treatment nausea, mean (SE)	1.1 (0.2)	1.4 (0.3)	0.6 (0.2)	1.2 (0.3)

Data might not add up to 100% because of rounding

SE standard error

[a] Acupressure bands + expectancy-enhancing relaxation music and written handout

[b] Acupressure bands + expectancy-neutral relaxation music and written handout

[c] Control

Primary analyses on effects of the expectancy manipulation

As specified in the protocol, patients in arm 1 were compared to patients in arm 2 for the primary aim. One hundred fifty (N) of the 161 patients randomized to arms 1 and 2 were included in the primary analysis (Fig. 2). The unadjusted means for peak CIN (primary outcome) for arms 1 and 2 were 3.52 (SE = 0.20) and 3.55 (SE = 0.23), respectively. Age, nausea susceptibility, motion sickness, morning sickness during

pregnancy, and expected worst level of CIN were significantly associated with peak CIN ($p \leq 0.03$), while expected band efficacy was not ($p = 0.774$).

No statistically significant group differences for peak CIN were observed between those receiving the expectancy-enhancing material and those receiving the expectancy-neutral material whether we did or did not control for abovementioned variables that were correlated with peak CIN (both p values > 0.05; Table 2).

The mean expected band efficacy for arms 1 and 2 was 3.45 (SE = 0.09) and 3.25 (SE = 0.10), respectively, with no significant group differences ($p = 0.144$). We also assessed if expected band efficacy changed after patients received the expectancy-enhancing/neutral material during randomization. The means for arms 1 and 2 were 3.95 (SE = 0.09) and 3.73 (SE = 0.10), respectively, with no significant group differences ($p = 0.122$).

Secondary analyses on effects of the intervention collapsing across arms 1 and 2

As stated in the "Methods," because of significant interactions, these analyses are stratified. Of the 226 patients, a higher proportion of those on doxorubicin had moderate-severe levels of peak CIN than those not receiving doxorubicin (72% vs. 57%; $p = 0.025$). Among patients receiving doxorubicin, acupressure bands with relaxation music significantly reduced peak CIN by 17% compared to controls (3.62 vs. 4.38; $p = 0.02$). However, there was no beneficial effect of the intervention for patients not receiving doxorubicin (Table 3; Fig. 3a).

Among 226 patients, those with high pre-treatment anxiety had significantly higher peak CIN than patients with low anxiety (3.96 vs. 3.35; $p = 0.017$). In patients with high anxiety, acupressure bands with relaxation music reduced peak CIN by 22% compared to controls (3.62 vs. 4.62; $p = 0.013$). No

positive effects of the intervention were seen for patients with low anxiety levels (Table 3; Fig. 3b).

We also found that acupressure bands with relaxation music, compared to controls, reduced peak CIN by 28% for those patients who received doxorubicin and also had high pre-treatment anxiety (3.63 vs. 5.01; $p = 0.008$; Table 3).

Satisfaction with band

The overall satisfaction with acupressure bands and relaxation music, as assessed by the feedback question asking whether they would recommend them to other chemotherapy patients, was positive with mean responses of 3.92 and 3.59, respectively. Seventy percent of patients thought the bands were somewhat or very useful in managing CIN. Additionally, 89% said the bands reduced their apprehension of side effects, while 74% said the same for relaxation music.

Discussion

In this large, phase II RCT of female breast cancer patients with high CIN expectancies, we did not find a significant difference between acupressure bands with expectancy-enhancing material designed to enhance the expectation of acupressure bands' efficacy and acupressure bands with expectancy-neutral material, when used as an adjunct to standard antiemetics, for reducing CIN. This is contrary to the preliminary study from our group, in which manipulation of efficacy expectancies for acupressure bands resulted in improved control of CIN in patients with high CIN expectancies [12].

The failure of the study to support our primary hypothesis was likely due to the fact that our manipulation technique via relaxation music and written handout was not successful in changing these efficacy expectancies. We did not find

Table 2 Comparison of peak chemotherapy-induced nausea by acupressure bands plus expectancy-enhancing or expectancy-neutral material

Coefficient	Mean difference	SE	p value	95% CI (mean difference)	ES	95% CI (ES)
Arm (1 vs. 2)						
Peak CIN	0.002	0.31	0.996	− 0.61 to 0.62	0.001	− 0.32 to 0.32
Peak CIN (after controlling for related covariates)[a]	− 0.19	0.29	0.510	− 0.77 to 0.38	− 0.10	− 0.42 to 0.22

Mean difference and associated statistics refer to adjusted differences between groups. Effect size (ES) is the standardized mean difference (Cohen's d); 95% CI is the lower and upper 95% confidence limits. Arm 1: acupressure bands + expectancy-enhancing relaxation music and written handout; arm 2: acupressure bands + expectancy-neutral relaxation music and written handout

SE standard error, *CIN* chemotherapy-induced nausea

[a] Covariates correlated with peak CIN for arms 1 and 2: age, nausea susceptibility, motion sickness, morning sickness during pregnancy, and expected worst level of CIN

Table 3 Comparison of peak chemotherapy-induced nausea for doxorubicin and anxiety levels

Coefficient	Mean difference	SE	*p* value	95% CI (mean difference)	ES	95% CI (ES)
Acupressure bands + relaxation music (yes vs. no)						
Doxorubicin and non-doxorubicin groups						
Peak CIN (doxorubicin group)	− 0.76	0.33	0.020	− 1.41 to − 0.12	− 0.40	− 0.74 to − 0.06
Peak CIN (non-doxorubicin group)	0.51	0.46	0.278	− 0.42 to 1.43	0.27	− 0.22 to 0.75
High and low pre-treatment anxiety groups						
Peak CIN (high anxiety group)	− 1.00	0.40	0.013	− 1.79 to − 0.22	− 0.53	− 0.93 to − 0.12
Peak CIN (low anxiety group)	0.21	0.36	0.556	− 0.50 to 0.93	0.11	− 0.27 to 0.50
Doxorubicin with high anxiety (yes/no)						
Peak CIN (doxorubicin with high anxiety = yes)	− 1.38	0.51	0.008	− 2.39 to − 0.37	− 0.72	− 1.21 to − 0.22
Peak CIN (doxorubicin with high anxiety = no)	0.17	0.31	0.576	− 0.44 to 0.79	0.09	− 0.25 to 0.43

Mean difference and associated statistics refer to adjusted differences between groups. Effect size (ES) is the standardized mean difference (Cohen's *d*); 95% CI is the lower and upper 95% confidence limits

SE standard error, *CIN* chemotherapy-induced nausea

significant group differences in expected band efficacy. Nor did we find group differences in changes in expected band efficacy after the expectancy material was provided. Additionally, we found no correlation between the expected band efficacy and CIN. This is in contrast to the generally accepted assumption that a positive expectancy is an essential element for placebo efficacy [24]. This may have occurred because the study selected for patients who expected CIN, and it is possible the magnitude of expected bands efficacy was not sufficient to affect CIN—a highly resistant symptom. Another possible explanation is that once generated, the placebo effect does not vary by dose. This possibility is supported by the findings of a study examining open-label placebo dose (one pill per day vs. four pills per day) on physical and psychological symptoms in 92 healthy undergraduates [25]. The authors found a placebo response but did not find a dose-response effect on symptom improvement. They concluded that open-label placebo responses may not be dose-dependent. Their lack of a dose-response effect may be similar to what we found in our present study i.e., we most likely generated a placebo effect through the use of acupressure bands and relaxation MP3 recordings but were unable to generate a dose-response effect by the additional use of written and verbal expectancy manipulations.

Interestingly, we found that acupressure bands and relaxation music, independent of the expectancy material, significantly improved CIN by 17% compared to controls for those patients who received a doxorubicin-based chemotherapy regimen, but not for patients who did not receive doxorubicin. Usually a 15−17% change in nausea is considered clinically significant improvement in many NCI-sponsored multicenter nausea trials [6, 26]. A large proportion of our patients (67%) received doxorubicin, and they as a group had greater CIN than the other patients, who did not receive doxorubicin. Doxorubicin, an anthracycline, is a commonly used

chemotherapeutic agent for breast cancer [27], and when used in combination with cyclophosphamide, as in 99% of our patient group, is considered highly emetogenic [28]. This is
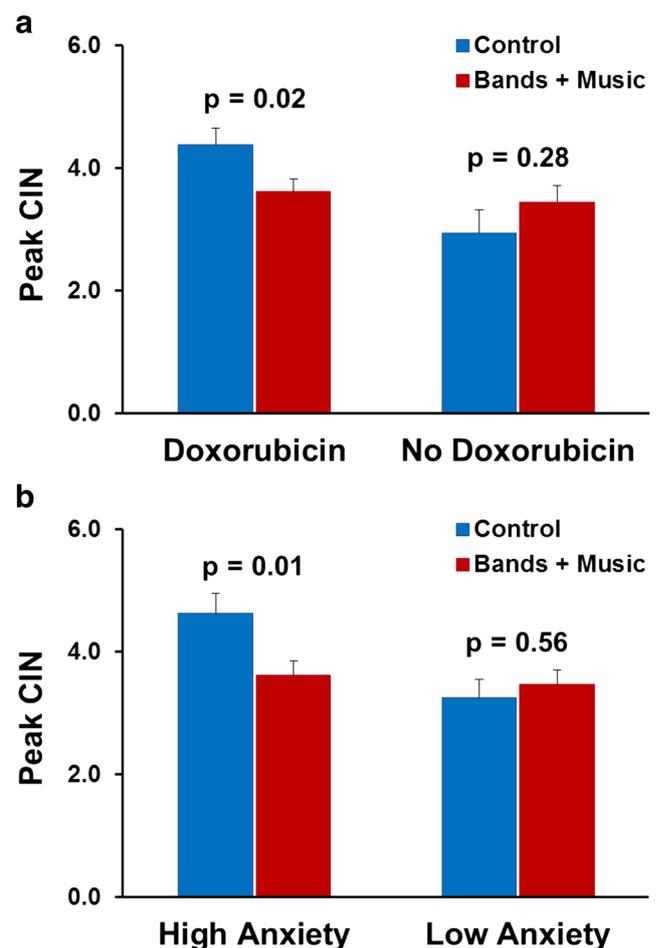

Fig. 3 Adjusted means for peak CIN by intervention groups for: **a** whether or not patients received doxorubicin-based chemotherapy, and **b** whether patients had high or low pre-treatment anxiety

consistent with previous studies that have also shown a benefit of acupressure bands in improving CIN in patients receiving chemotherapy of moderate/high emetogenicity [5, 7, 8, 11].

We do not truly know why the patients not receiving doxorubicin showed no benefit from the bands or music. We speculate that it may be related to a dynamic in the cancer clinic due to a general belief held by the clinic nurses that patients receiving doxorubicin will have greater CIN than other patients. We speculate that such expectancies are somehow transferred to patients, and that it is this type of transferred expectancy that increases both anxiety and CIN and is somewhat countered by the acupressure bands and relaxation music.

This speculation is supported by our finding that the acupressure bands combined with relaxation music, independent of the expectancy material, significantly reduced CIN by 22% compared to controls for those patients who had high anxiety, but not for those who had low anxiety. To the best of our knowledge, no previous study has examined the differential effects of acupressure bands and relaxation music on CIN based on patients' level of anxiety. Anxiety is believed to contribute to CIN, partly through negative expectations, although the relationship between anxiety and negative expectations appears to be bi-directional [4]. In our overall study sample, we did find a significant association of anxiety with both CIN expectancies and CIN. Previous research has also shown that acupressure is effective in decreasing anxiety in breast cancer patients [10]. Thus, indicating that for our study, the significant effect of acupressure in reducing CIN was probably through improvement in anxiety. We also found that those patients who received doxorubicin and had high anxiety saw even a greater reduction in CIN with acupressure bands and relaxation music compared to controls, further confirming the beneficial effects of the intervention in this high-risk group.

The strengths of our study include the large sample size, being multicenter, and the randomized and blinded design. Nevertheless, the following limitations should be considered when interpreting the results from this study. First, the 5-day diary measure of CIN is not a validated measure, although it has been previously utilized by many large nationwide clinical trials on CIN for over 20 years. Second, findings are limited to the population studied: female breast cancer patients receiving moderately or highly emetogenic chemotherapy, who expected CIN, and who were predominantly white and non-Hispanic. The results of this study cannot be generalized to women with different racial and ethnic backgrounds, acupressure at acupoints other than P6, or to other methods of acupoint stimulation (e.g., electric acustimulation). Lastly, since the relaxation music was always included with the acupressure bands, we do not know the effects of the individual components. This study nonetheless has important clinical implications for an important subset of patients. That is for

patients with breast cancer who expect CIN and either will receive doxorubicin and/or who have anxiety prior to treatment. For such patients, acupressure bands with relaxation music had significant beneficial effects on reducing CIN. Future research should evaluate the individual contributions from the bands and the relaxation music.

Conclusion

In breast cancer patients undergoing chemotherapy and having high expectation of CIN, an attempt to increase the efficacy of acupressure bands in controlling CIN through manipulation of expected efficacy was not successful. However, acupressure bands with relaxation music differentially impacted CIN based on patients' type of chemotherapy regimen or level of anxiety and significantly reduced CIN for those who received anthracycline and/or had high anxiety. Considering that receiving doxorubicin and having anxiety are known predictors of CIN, it appears that our intervention had the serendipitous finding of working best for patients who needed it most. Our study provides support for the use of acupressure bands along with relaxation music as a safe and non-invasive adjunct to standard antiemetics for controlling CIN in breast cancer patients who receive anthracycline and/or have anxiety.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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