Original Article

Acustimulation Wrist Bands Are Not Effective for the Control of Chemotherapy-Induced Nausea in Women with Breast Cancer

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Abstract
This experiment examined the efficacy of an acustimulation wrist band for the relief of chemotherapy-induced nausea using a randomized three-arm clinical trial (active acustimulation, sham acustimulation, and no acustimulation) in 96 women with breast cancer who experienced nausea at their first chemotherapy treatment. Five outcomes related to wrist band efficacy (acute nausea, delayed nausea, vomiting, QOL, and total amount of antiemetic medication used) were examined. The five outcomes were examined separately using analysis of covariance controlling for age and severity of past nausea. There were no significant differences in any of these study measures among the three treatment conditions ($P > 0.1$ for all). Study results do not support the hypothesis that acustimulation bands are efficacious as an adjunct to pharmacological antiemetics for control of chemotherapy-related nausea in female breast cancer patients. J Pain Symptom Manage 2005;29:376–384.

Key Words
Nausea, chemotheraphy, acustimulation, antiemetic, acupuncture

Introduction

The 5-HT_3 antagonists, in widespread use since the early 1990s, are more effective than prior medications in preventing chemotherapy-induced vomiting.[1–3] However, chemotherapy-related nausea is not as well controlled by these drugs and remains a significant problem.[3] In one community-based study involving 1,413 cancer patients undergoing chemotherapy, 80% experienced nausea to some degree, with 40% having at least one episode of vomiting.[3] Similarly, in a recent study published by our group, 76% of 322 patients who received chemotherapy regimens containing cisplatin, carboplatin, or doxorubicin experienced nausea

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following their first treatment, despite what was felt by physicians to be adequate antiemetic prophylaxis. Of these 322 patients, 147 (46%) had nausea of moderate severity or greater.[4] Uncontrolled nausea and vomiting (NV) seriously detract from quality of life (QOL),[5–7] can interfere with adherence to treatment regimens, and may cause oncologists to reduce chemotherapy doses.[8–10] Identifying methods to successfully prevent and alleviate treatment-related nausea remains a major clinical challenge.

Theory and clinical experience suggest that the complementary and alternative medicine treatment of acupuncture point stimulation could affect NV from chemotherapy. Stimulation of the P6 acupuncture point located on the inside of the wrist with needles (acupuncture) or pressure (acupressure) has been used to relieve NV in traditional Chinese medicine for centuries.[11] Recent literature reviews indicate that acupuncture and acupressure may provide relief from these symptoms.[12–14] Specifically, needling or applying pressure (generally with an acupressure band such as the SeaBand, Sea Band UK Ltd., Leicestershire, England) to an acupoint have been efficacious in alleviating morning sickness,[15–18] motion sickness,[19,20] post-surgical nausea,[21–27] and NV associated with chemotherapy.[28,29]

Beginning in the early 1990s, studies assessing the efficacy of mild electrical stimulation (acustimulation) using portable TENS wrist bands to the P6 acupuncture point for control of nausea have also been conducted. All of these studies used the ReliefBand (Figure 1; Woodside Biomedical, Carlsbad, CA), which is marketed for this purpose and has United States Food and Drug Administration (FDA) clearance as treatment for NV due to pregnancy, motion sickness, and chemotherapy, and as an adjunct to antiemetics for post-operative nausea. Positive findings have been found for the efficacy of acustimulation bands in controlling motion sickness,[30] morning sickness,[31–34] and postoperative nausea.[35–37]

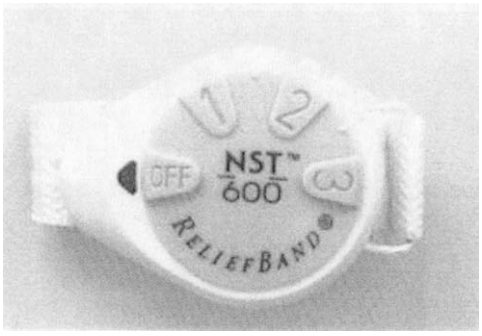

Fig. 1. ReliefBand, Woodside Biomedical, Carlsbad, CA.

A literature review revealed five publications on the efficacy of acustimulation bands for the treatment of chemotherapy-induced nausea. Treish and colleagues[38] conducted a randomized study in which 50 patients wore either active or placebo acustimulation bands for five days after chemotherapy as an adjunct to standard antiemetic medications. Those wearing the active band reported significantly less nausea and significantly fewer episodes of vomiting compared to patients wearing the placebo bands. Pearl and colleagues[39] conducted a randomized, double blind, placebo-controlled experiment with a follow-up crossover trial. Of the 18 patients completing the crossover portion of the study, those who wore the active band, as compared to the placebo band, reported significantly less severe nausea on the second through fourth post-treatment days.

The other three studies were conducted by our own research group. In the first of these, the results closely approached conventional levels of statistical significance ($P < 0.06$) when the efficacy of the bands in reducing the severity of delayed nausea were compared to no bands in 27 chemotherapy recipients who had experienced nausea after their first treatment.[40] This finding must be interpreted with particular caution, however, because of weaknesses associated with the 3-level crossover design used in the study. Our second study was a non-controlled, open-label trial in which we gave Reliefbands to 42 patients who had nausea at their previous two chemotherapy treatments.[41] Sixteen of the 29 patients who completed the optional feedback questionnaire following treatment said the band was somewhat or very helpful in reducing nausea.

Finally, our group conducted a large multicenter study that directly compared the effectiveness of acustimulation bands versus acupressure bands (SeaBand), as an adjunct to 5-HT_3 receptor antagonist antiemetics given as part of routine care.[29] A total of 739 (male = 57) patients scheduled to begin their first treatment with

either cisplatin or doxorubicin were randomly assigned to wear bilateral SeaBands, one Reliefband, or no band. Pronounced gender differences in efficacy were found. Fewer men vomited in the Reliefband (16%) compared to the no band (50%) condition ($P = 0.03$). Men who wore the Reliefband also experienced less nausea on the day of treatment ($P < 0.05$) and less nausea overall ($P < 0.05$). There were no significant differences in any outcome measures between the acustimulation and the acupressure treatment conditions. By contrast, the acustimulation band was not helpful for women. The reduction in nausea on the day of treatment in the acupressure band compared to the no band condition, however, closely approached statistical significance ($P = 0.052$).

Interestingly, when expected efficacy of the wrist bands was considered, differences in the severity of nausea by whether or not patients thought the bands would be effective were observed in those patients assigned to the acupressure condition, but not for those in the acustimulation condition. Patients who received the acupressure bands and expected them to be effective ($n = 112$) experienced less nausea on the day of treatment and also less overall nausea compared those who did not expect them to be effective ($n = 121$) and to the no band control group ($n = 233$) ($P < 0.05$ for all).

The current study adds to this somewhat mixed literature on the effectiveness of acustimulation bands for control of chemotherapy-induced nausea with a randomized three-arm clinical trial examining the efficacy of the Reliefband as an adjunct to standard 5-HT_3 antiemetics. Unlike previous studies examining the efficacy of the device in cancer patients, the present study used a homogenous sample in which all participants were the same sex (female), had the same diagnosis (breast cancer), and received the same chemotherapy regimen (doxorubicin and cyclophosphamide). This is also the only study examining the efficacy of acustimulation bands that used a parallel arm study design with an active band in the placebo control condition. With the exception of a small 9-patient crossover study,[30] all prior studies examining the efficacy of the bands either did not use a placebo control condition or used an inactive band as the placebo control. The use of an active acustimulation band in the sham location condition was intended to more adequately control for the placebo effect as well as for any effect due to the release of endorphins from the electrical stimulation, thereby allowing us to directly examine the efficacy of acupuncture point stimulation. In addition, the experiment had a "no band" condition for additional comparisons.

Methods

Patients

Women with breast cancer 18 years of age or older who were about to receive their second doxorubicin-based chemotherapy treatment at one of four Rochester area cancer centers and who experienced nausea and/or vomiting after their first chemotherapy cycle were potentially eligible to participate. Patients with clinical evidence of bowel obstruction, symptomatic brain metastases, or who were using a cardiac pacemaker or undergoing concurrent radiotherapy or interferon treatment were excluded. Written informed consent was obtained from each subject and the Institutional Review Board of each participating site approved the protocol.

Procedures

To encourage patient participation and promote patient confidence in the project, the medical oncologist of each potential participant briefly explained the study to eligible patients. S/he then introduced the patient to the study personnel, all of whom had been trained in the proper use of the Reliefband, for a more complete description of the study. Participants who agreed to participate were immediately randomized to one of three treatment arms. Patients assigned to wear the band in the sham location placed it on the outside of the wrist approximately 2 inches proximal to the crease of the wrist. Those assigned to wear it in the correct location placed it on the inside of the wrist, approximately 2 inches proximal to the crease of the wrist joint between the tendons of the palmaris longus and flexor carpi radialus muscles. Patients were told that we were examining the efficacy of stimulation to acupuncture points on both the inside and outside of the wrist. At no point did we ever use the word sham or placebo when describing the study procedures to patients.

All patients assigned to wear an acustimulation band were told they could adjust the intensity of the stimulation by turning the dial to the intensity setting, from 5 possible positions ranging from 10 to 35 mA, that they felt was the most comfortable and/or effective. Data were not collected on intensity settings chosen by study participants. They also were told to avoid letting the band come into contact with water. They could wear the band on either wrist, provided the arm was not affected by lymphedema. Patients were instructed to wear the band as much or as little as they wanted or needed to over the five days of the study, and to keep track of the total number of hours they wore the band.

All patients received standard clinical antiemetic prophylaxis, which included a 5-HT_3 receptor antagonist antiemetic on the day of treatment. Dexamethasone or another corticosteroid was allowed, as were all ancillary treatments as appropriate for control of symptoms of the cancer or the side effects of its treatment. All antiemetic medications taken over the five days following treatment were recorded in a medication log maintained by the patient.

Measures

At the time of consent, patients provided demographic information and details concerning prior experience with NV, for example, nausea during pregnancy, susceptibility to motion sickness, and so on. Patients were also asked to describe their nausea at its worst following their previous treatment. The possible responses were "very mild or none at all," "mild," "moderate," "severe," "very severe," and "intolerable." These responses were coded 1–6, respectively.

Expected efficacy of the Reliefband in controlling nausea following the second chemotherapy infusion was assessed using a 5-point scale anchored at one end by 1 = "Not at all effective" and at the other end by 5 = "Very effective." This assessment was made at the time of randomization following a one-minute trial application of the band turned on and placed in the position determined by the condition to which the patient had been randomized.

Nausea and emesis were measured by a patient report diary, based on one developed by Burish[42] and Carey,[43] that was completed by patients over a five-day period. Each day was divided into four segments (morning, afternoon, evening, night) in each of which patients reported the severity of nausea and number of vomiting episodes for each period on the day of treatment and on the four following days. Severity of nausea was assessed on a 7-point rating scale, anchored at one end by 1 = "Not at all nauseated" and at the other end by 7 = "Extremely nauseated." Anti-nausea medication use and number of vomiting episodes were recorded for the same time intervals as part of the diary. Additional questions concerning use of and recommendations for the acustimulation band were added to the measure.

Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy Scale–General (FACT–G). The FACT–G is a 28-item scale (higher scores = better QOL) developed specifically for use in cancer clinical trials.[44] It was developed by Cella and his group through extensive interviews with patients experiencing cancer- or treatment-related symptoms and with oncology professionals. It has shown very good test–retest reliability as well as validity.[45] Patients completed the measure four days after the day of chemotherapy and assessed QOL retrospectively since the treatment began.[46]

Participants were given the latter two questionnaires to complete at home, with instructions to mail them back in the stamped, pre-addressed envelopes that were provided. Reminder phone calls were made to patients, if necessary. The study concluded with the return of data following the second chemotherapy treatment.

Planned Analyses

The primary outcome variable for this study was the severity of nausea averaged across days 2–5 of treatment, that is, delayed nausea. Analysis of variance (ANOVA), with a significance level of 0.05, was used to compare the average nausea severity between the three treatment arms. We intended to compare the sham location group to the correct location group if the previous analysis was significant. Secondary study outcomes were the severity of nausea during the first 24 hours following chemotherapy (acute nausea) and the occurrence of vomiting during the same 24-hour period. Data for acute nausea were analyzed in the same way as

delayed nausea. Occurrence of vomiting was analyzed using a logistic regression model parallel to the ANOVA model used to analyze severity of nausea. All analyses were done on an intent-to-treat basis.

A further objective of this study was to determine if expected efficacy of the acustimulation band was related to actual band efficacy. In addition to the above, exploratory analyses were planned with QOL and amount of antiemetic medication used as the outcome variables.

Results

Patient Sample

Ninety-six (90%) of the 107 patients randomized to the study provided evaluable data. Of these 96 patients, 87 were white, 8 were African-American, and one participant self identified as "other." Age ranged from 28–72 years, with a mean of 49.5, and most (72%) were married. Thirty-three patients were randomized to the control condition (no band); 31 were assigned to the incorrect location condition (outside of wrist); and 32 were randomized to wear the band in the correct location (inside of wrist). All study subjects received their treatments as outpatients. Eighty-nine of the 96 patients took some type of antiemetic following treatment; 6 took none, and the data from one patient regarding antiemetics are missing.

ANOVA showed that the three study arms did not differ significantly by susceptibility to motion sickness, nausea during pregnancy (yes, no, or not applicable), optimism, or any of the other questions relating to susceptibility to NV (all Ps > 0.1). Despite randomization, the groups did, however, differ by age ($\text{mean}_{\text{no band}} = 50.6$, $\text{mean}_{\text{sham}} = 45.4$, $\text{mean}_{\text{correct}} = 52.4$, $P = 0.008$) and by the degree of nausea experienced following the prior treatment ($\text{mean}_{\text{no band}} = 4.0$, $\text{mean}_{\text{sham}} = 3.2$, $\text{mean}_{\text{correct}} = 3.0$, $P < 0.001$). These two variables were, therefore, used as covariates in all analyses examining outcome difference between treatment arms.

Mean nausea severity scores were calculated from the last two reporting periods on day 1 (for acute nausea) and from the 16 reporting periods from days 2–5 (for delayed nausea). Data from the morning and evening of day 1 were excluded because patients may not have completed their infusions before late afternoon. Missing data were minimal and not extrapolated.

Treatment Effects

Five outcomes related to wrist band efficacy (acute nausea, delayed nausea, any vomiting, QOL, and total amount of antiemetic medication used) were examined using analysis of covariance (ANCOVA) controlling for age and past nausea severity. There were no significant differences in any of these study measures among the three treatment conditions (all Ps > 0.1) (Table 1).

Treatment Effects by Expected Band Efficacy

A t-test for independent samples showed that mean expected efficacy for the acustimulation bands using the full 5-point scale did not differ by band placement ($\text{mean}_{\text{sham}} = 3.45$, $\text{mean}_{\text{correct}} = 3.47$, $P = 0.9$). Similarly, expected efficacy for the device was not significantly correlated with age ($r = 0.02$), nor with peak severity of nausea from the prior treatment ($r = -0.09$, both Ps > 0.3). Because no differences were observed in actual or expected band efficacy related to band placement location, data from patients in the two trial arms receiving the bands were combined and a new grouping for these patients, based upon expected band efficacy, was created. Consistent with methodology from our multicenter study discussed earlier, the 26 patients who indicated a response of either "4" or "5" on the expected efficacy question were coded as "high expected efficacy" and the remaining 37 patients receiving the acustimulation bands were coded "low expected efficacy." Differences in the study outcome variables (acute nausea, delayed nausea, any vomiting, QOL, and total amount of antiemetic medication used) between these two groups were then examined using t-tests for independent samples. No statistically significant differences between groups were observed for any of the outcome measures (all Ps > 0.5).

Satisfaction with Band and Duration of Use

Overall satisfaction with the acustimulation bands appeared to be high, with more than one-third of the patients wearing the band for over 48 hours (the longest of the five "duration of time worn" categories on the feedback questionnaire) and over 60% wearing the band at

Table 1
Comparison of Study Outcomes by Randomization Condition

	No Band ($n = 33$) Mean (SE)	Sham Location ($n = 31$) Mean (SE)	Correct Location ($n = 32$) Mean (SE)
Delayed nausea[a]	2.8 (0.23)	2.4 (0.23)	2.6 (0.23)
Acute nausea[b]	2.4 (0.28)	2.2 (0.28)	2.2 (0.28)
Quality of life	71.1 (2.4)	77.6 (2.4)	75.4 (2.4)
Vomiting[c]	39%	26%	44%
Pill count[d]	10.9 (1.4)	11.8 (1.4)	9.0 (1.4)

Differences between groups are not statistically significant, all Ps > 0.1; values reported for nausea and QOL are estimated marginal means (controlling for age and nausea severity from the prior treatment).
[a]Average for treatment days 2–5.
[b]Average for day 1 of treatment.
[c]Proportion of patients who vomited.
[d]Total number of antiemetic pills taken.

least 24 hours. The proportion of patients wearing the bands at least 24 hours was somewhat higher in the correct location compared to the sham location group (72% vs. 53%). Overall patient satisfaction with the band was moderate as assessed by the feedback question asking whether they would recommend that other patients wear a band when receiving chemotherapy. The mean response on this 5-point scale (anchored at one end by 1 = "Strongly do not recommend" and at the other end by 5 = "Highly recommend") was 3.3. The slight difference in strength of recommendation by location (means: sham = 3.2, correct = 3.4) was not statistically significant ($P = 0.34$).

Discussion

Our results do not show that acustimulation bands are efficacious when used as an adjunct to pharmacological antiemetics for the control of chemotherapy-related NV in female breast cancer patients. There were no statistically significant differences between groups for any of the five outcome measures-delayed nausea, acute nausea, vomiting, QOL, and amount of antiemetic medication taken. These findings are in keeping with the results of our multicenter study, which ran concurrently with this one, comparing the efficacy of acupressure bands with acustimulation bands for control of chemotherapy-induced nausea. This multicenter study, as discussed previously, also found no evidence that the acustimulation bands were beneficial to women. Interestingly, although not helpful for women, the device was helpful to the men in that study.

Our current findings that the acustimulation bands were not helpful held true even for the women who thought the bands would be efficacious. The 26 women who received an acustimulation band and expected the device to be helpful fared no better than the 37 women who received a band and held neutral or negative expectancies. Expectation of efficacy for a treatment, thought to be a primary component of the placebo effect,[47,48] has been related to the efficacy of acupressure bands[22,29,49] and could reasonably have been expected to be related to acustimulation band efficacy. The finding that control of NV did not improve even for the subgroup of women who expected the acustimulation bands to be effective is, however, in keeping with the results of the above mentioned multicenter study. The apparent placebo effect associated with use of the acupressure bands found in that study was not present for women receiving the acustimulation bands.[29]

Although the negative results from the current study concerning acustimulation band efficacy are in complete agreement with the findings from the subgroup of women in the multicenter study who received the device, they are difficult to reconcile with other published research. All of the other published research reported efficacy for the device in controlling at least some aspect of nausea or vomiting. Adding to this perplexity is the fact that the acustimulation band, although not efficacious for women in the multicenter study, was very helpful for men. Although evidence from the multicenter study suggests the existence of a sex difference, this is certainly not the only factor involved, as no other investigation examining acustimulation bands reported a sex effect and several of the prior positive studies had only female participants.[31–34,39]

A possible explanation for discrepancy in the findings from published studies is that the effectiveness of acustimulation bands may vary according to the etiology of nausea under investigation. Chemotherapy-induced nausea may simply be more difficult to control than nausea following surgery, from motion, or during pregnancy. This explanation fits with most of the published data, as it is only in our two studies involving chemotherapy that the bands were found to be ineffective. Taking this line of reasoning one step further, it is also possible that nausea from a given chemotherapy agent, namely, doxorubicin, may not be amenable to control through acustimulation. Doxorubicin, a drug commonly given to breast cancer patients, is known to be a highly emetogenic drug,[4] and all of the women in the current study and most of the women in the multicenter study received a relatively high dose of this agent. Few of the men in the multicenter study, even if they received doxorubicin, would have received as high a dose as the women received, because typically this drug is given in lower doses when used to treat cancers other than breast cancer. Unfortunately, the two other investigators examining acustimulation band efficacy in chemotherapy patients did not provide enough information in their reports to determine if the type of chemotherapy agent played a role in the efficacy of the device.[38,39]

A seeming anomaly in our results is the finding of no statistical benefit in our outcome measures even though patient acceptance of the acustimulation bands was generally high, as evidenced by the fact that more than 60% of the patients voluntarily wore the device for at least 24 hours. We speculate that this incongruity may in part be due to a potential problem that, in some circumstances, can cause patients using the acustimulation bands to feel worse. Patients who develop nausea while wearing the acustimulation band may be subjected to a negative conditioning effect, with the band becoming a reminder and reinforcer of their unpleasant state. This view is supported by our data from the multicenter study showing that women randomized to wear the acustimulation band not only reported no benefit but actually reported significantly more nausea on Day 3 than patients in the control group.[29] A simple way to avoid this potential conditioning problem, which we unfortunately did not do in either study but would recommend for all patients receiving an acustimulation band, is to instruct them to take it off if nausea develops. They should then experimentally determine if the band is helpful by putting it back on after a short period of time and leaving it on only if they felt better with it on. Any conditioning effect present would then be positive in nature because wearing the band would then be associated with feeling better.

Further research will be needed to determine if the effectiveness of the acustimulation band is dependent upon the specific cause of the nausea being treated and if there are specific chemotherapy agents or categories of patients, for example, males, for whom the device is effective.

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