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Exploring Chemotherapy-Induced Nausea and Vomiting:
The Symptoms, Interventions, and Relationship to Functional Status

by

Jiyeon Lee, RN, MS

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

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by

Jiyeon Lee

Acknowledgement

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This dissertation is organized in four chapters that include one paper that has been accepted for publication by *the Journal of Pain and Symptom Management*, one to the *Oncology Nursing Forum*, one that has been published in *Cancer Nursing*, plus one paper that will be submitted for publication. Chapter 1 is a reprint of the accepted version of the article in the *Journal of Pain and Symptom Management*. The manuscript in Chapter 2 will be submitted for publication. Dissertation committee members will be listed as co-authors in this manuscript. Chapter 3 is a reprint of the accepted version of the article in *Oncology Nursing Forum*. Chapter 4 is a reprint of the material as it appears in *Cancer Nursing*, 2005, 28(4), 249-255. The work that Jiyeon Lee completed through four chapters was sufficient to meet all UCSF, Graduate Division, and School of Nursing dissertation requirements relating to the use of published data and relating to the requirements associated with the graduating student having been primarily responsible for writing and revising the dissertation material.

A handwritten signature in cursive script that reads "Marilyn J. Dodd". The signature is written in black ink and is positioned above a horizontal dotted line.

Marilyn Dodd, RN, PhD, FAAN

Dissertation Committee Chair

Exploring Chemotherapy-Induced Nausea and Vomiting:
The Symptoms, Interventions, and Relationship to Functional Status

Jiyeon Lee

Abstract

Background: Chemotherapy-induced nausea and vomiting (CINV) has been acknowledged as the most distressing symptom caused by chemotherapy. Symptom control by antiemetics in the delayed phase, and especially nausea control has been unsatisfactory and the side effects from the antiemetics have impelled researchers to investigate additional non-pharmacologic interventions for CINV control. The influence of CINV on patients' functional status has been reported, however, the relationship between CINV and their functional status during chemotherapy is understudied.

Purpose: This dissertation is aimed at adding to the knowledge base related to the experiences with and influences of CINV and to the additional interventions for CINV control such as P6 acupressure and aerobic exercise. The specific purpose includes 1) evaluating the effects of acupressure through literature review when acupressure was combined with antiemetics for the control of CINV. 2) exploring the experience of chemotherapy-induced nausea (CIN) in relation to the frequency of P6 digital acupressure in a group of breast cancer patients who had received moderate to highly emetogenic chemotherapy plus applied P6 digital acupressure as an additional intervention for CIN. 3) evaluating the relationship between nausea and a moderate level of aerobic exercise during and after adjuvant cancer treatment for women with breast cancer. 4) determining the relationship of CINV to the functional status of women undergoing chemotherapy for breast cancer treatment.

Methods: A literature review evaluated the effect of P6 acupressure for CINV control. Three data-based studies were conducted using three existing data sets from larger studies. The first study examined the relationship of CIN to the frequency of P6 digital acupressure. The second study evaluated the relationship of nausea and a moderate level of aerobic exercise. The third study explored the relationship between CINV and functional status during chemotherapy.

Findings: CINV, especially in the delayed phase, and nausea is an important clinical issue that may influence functional status of patients. The use of P6 acupressure and performing a moderate level of aerobic exercise are suggested interventions for CINV control. However, further study is clearly needed.

Word count: 333

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) has been acknowledged as the most distressing symptom caused by chemotherapy. New understandings about serotonin related mechanisms and the development of 5-hydroxytryptamine receptor antagonists (5-HT₃ RAs; ondansetron, granisetron, and dolasetron) in 1990s advanced the control of CINV considerably. The approval of neurokinin-1 receptor antagonist (NK-1 RA; aprepitant) and the second generation 5-HT₃ RA (palonosetron) in 2003 by the Food and Drug Administration (FDA) initiated a new era for CINV control. Oncology organizations such as the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer Network (NCCN) have published updated antiemetic guidelines for optimal control of CINV (Kris et al., 2006; NCCN, 2008; Roila, Hesketh, & Herrstedt, 2006). The employment of antiemetics according to the newest antiemetic guidelines has significantly improved the control of chemotherapy-induced vomiting (Hesketh et al., 2003; Poli-Bigelli et al., 2003).

However, the symptom of chemotherapy-induced nausea (CIN) requires further attention. Up to 61% of patients reported experiencing CIN even when the symptom is controlled with routine antiemetics (Molassiotis et al., 2008). Forty-seven percent of patients still experienced the symptom while using a combination of the two newest antiemetics, aprepitant and palonosetron (Grote et al., 2006). Patients now rank CIN as the most distressing side effect of chemotherapy (de Boer-Dennert et al., 1997; Lindley et al., 1999). This is not surprising as the mechanisms of nausea are still unclear, and the

development of antiemetics and antiemetic guidelines have been focused on the control of vomiting rather than nausea (Herrstedt, 2008).

CINV in delayed phase which begins and persists for more than 16 to 24 hours after chemotherapy administration, is also an issue (Lindley et al., 2005). The incidence of delayed symptoms has always been higher than that of acute symptoms (Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Fabi et al., 2003; Grunberg et al., 2004; Lindley et al., 2005; Molassiotis et al., 2008). The mechanisms for delayed symptoms were also less well understood other than the mechanism of substance P and the NK-1 receptor to delayed vomiting after highly emetogenic chemotherapy. More unsatisfactory is health care professionals' underestimation of the incidence of delayed symptoms (Grunberg et al., 2004; Liau et al., 2005).

Reported ineffectiveness of the recommended antiemetics in controlling symptom in delayed phase, especially nausea as well as the considerable side effects of antiemetics, such as headache and constipation from 5-HT₃ RA (Kovac, 2003), and asthenia and fatigue from NK-1 RA, (Dando & Perry, 2004) has urged researchers to find non-antiemetic, additional interventions to improve the control of CINV. The high cost in utilizing the recommended antiemetics and non-adherence to the recommended antiemetic guidelines in clinical practice also suggests the need to consider additional interventions that are more cost-effective, free of side-effects and easy to perform.

The influence of CINV on patients' functional status has been reported, however, the relationship between CINV and their functional status during chemotherapy is understudied.

This dissertation is aimed at adding to the knowledge base related to the experience and influence of CINV and to the additional interventions for CINV control such as P6 acupressure and aerobic exercise. The main body of the dissertation is organized in four chapters that include one paper that has been accepted for publication by *the Journal of Pain and Symptom Management*, one to *the Oncology Nursing Forum*, one that has been published in *Cancer Nursing*, plus one paper that will be submitted for publication. A summary of the dissertation will follow after these four chapters.

The first chapter of the dissertation is titled “Review of Acupressure Studies for Chemotherapy-Induced Nausea and Vomiting Control”. This literature review was accepted by the *Journal of Pain and Symptom Management* and is waiting for a scheduled publication date. This chapter is a reprint of the accepted version of the article. P6 acupressure has been investigated as an additional intervention for CINV control (Dibble, Chapman, Mack, & Shih, 2000; Dundee & Yang, 1990a, 1990b; Lo, 1998; Meyer, 2001; Noga, 2002; Price, 1992; Roscoe et al., 2006; Roscoe, Morrow, Bushunow, Tian, & Matteson, 2002; Shin, Kim, Shin, & Juon, 2004; Stannard, 1989). Recent studies have supported the benefit of using P6 acupressure to control CINV (Dibble et al., 2007; Ezzo et al., 2005; Molassiotis, Helin, Dabbour, & Hummerston, 2007; Roscoe et al., 2003), however there were result discrepancies as to when the P6 acupressure exerted its effect (Dibble et al., 2007; Roscoe et al., 2003). Careful review of P6 acupressure studies was strongly recommended to evaluate P6 acupressure as an additional intervention for CINV control. Study designs, methodological issues, and important factors of CINV that may confound the evaluation of acupressure effects were considered in this review. This literature review will improve the understanding about the effects of P6 acupressure in

control of CINV, will help recognize important issues in P6 acupressure trials that had limited final conclusions about the effects of P6 acupressure, and will also present future research directions for P6 acupressure trials.

The second chapter of the dissertation is titled “The Relationship of Chemotherapy-Induced Nausea to the Frequency of P6 Digital Acupressure”. This data-based paper will be submitted for publication. Details about CIN control in relation to the P6 acupressure needs to be explored as nausea continues to be of great concern with chemotherapy administration. This study explored the experience of CIN over 11 days in relation to the frequency of P6 digital acupressure in a group of breast cancer patients who received moderate to highly emetogenic chemotherapy and applied P6 digital acupressure as an additional intervention for CIN. Details about the utilization of P6 digital acupressure and corresponding changes in CIN were described and the relationship between the frequency of P6 digital acupressure and CIN was examined.

The third chapter of the dissertation is titled “Nausea at the End of Adjuvant Cancer Treatment is Related to Exercise during the Treatment in Breast Cancer Patients”. This data-based study was presented at the 32nd Oncology Nursing Society Congress. The text of this chapter is a pre-publication draft accepted for publication to the *Oncology Nursing Forum*, copyrighted 2008 to the Oncology Nursing Society (upon publication). Please see the printed journal for the final published article. This study expanded the scope of nausea into nausea during and after the chemotherapy and evaluated its relationship with aerobic exercise. Aerobic exercise was recognized as a possible intervention for nausea control, but with inconsistent results from a limited number of trials (Andersen et al., 2006; Mock et al., 1994; Schwartz, 2000; Winningham &

MacVicar, 1988). Considering the widely recognized benefit of aerobic exercise in cancer-related symptoms such as fatigue (Mitchell, Beck, Hood, Moore, & Tanner, 2007; Mock et al., 2005; Mock et al., 2001; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a, 2007b), it was more of question whether aerobic exercise could help alleviating nausea. This data-based study evaluated the relationship between nausea intensity and a moderate level of aerobic exercise recommended by the American College of Sport Medicine (1998) during and after adjuvant cancer treatment (chemotherapy +/- radiation therapy).

The fourth chapter of the dissertation is titled, “Chemotherapy-Induced Nausea/Vomiting and Functional Status in Women Treated for Breast Cancer”. The text of this chapter is a reprint of the material as it appears in *Cancer Nursing*, 2005, 28(4), 249-255 (Lee, Dibble, Pickett, & Luce, 2005). This study determined the relationship of CINV to the functional status of women undergoing chemotherapy for breast cancer over two cycles of chemotherapy. Changes in CINV and functional status over 11 days were evaluated and the relationships were examined.

Finally the summary of the dissertation is presented. Key findings of the studies presented in the previous four chapters are summarized and the implications for the care of patients with CINV are discussed. Directions for future research for the care of patients with CINV are addressed.

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Chapter 1.

Review of Acupressure Studies for Chemotherapy-Induced Nausea and Vomiting Control

Lee, J., Dodd, M., Dibble, S., & Abrams, D.

Journal of Pain and Symptom Management, in press

Abstract

The purpose of this review was to evaluate the effects of the non-invasive intervention, acupressure, for chemotherapy-induced nausea and vomiting (CINV) control in addition to antiemetics. Ten controlled acupressure studies were included in this review. The review evaluated one quasi-experimental and nine randomized clinical trials which included two specific acupressure modalities, i.e. acupressure band and finger acupressure. The effects of the acupressure modalities were compared study by study. Four of seven acupressure band trials supported the positive effects of acupressure, whereas three acupressure band trials yielded negative results regarding the possible effects of acupressure; however, all the studies with negative results had methodological issues. In contrast, one quasi-experimental and two randomized finger acupressure trials all supported the positive effects of acupressure on CINV control. The reported effects of the two acupressure modalities in each phase of CINV produced variable results. Acupressure bands were effective in controlling acute nausea, whereas finger acupressure controlled delayed nausea and vomiting. The overall effect of acupressure was strongly suggestive but not conclusive. Differences in the acupressure modality, the emetic potential of chemotherapeutic agents, antiemetic use, and sample characteristics of each study made study to study comparisons difficult. Suggestive effects of acupressure, cost-effectiveness, and the non-invasiveness of the interventions encourage researchers to further investigate its efficacy. Acupressure should be strongly recommended as an effective, non-pharmacologic adjuvant intervention for CINV control if its positive effects are reproduced in future acupressure clinical trials.

Key Words: Acupressure, chemotherapy, nausea, vomiting

Introduction

Recent advances in understanding the mechanisms of chemotherapy-induced nausea and vomiting (CINV) have led to the development of effective antiemetics, such as 5-HT₃ and NK-₁ receptor antagonists (RAs), and to the development of antiemetic guidelines for effective CINV control (Kris et al., 2006; NCCN, 2007; Roila, Hesketh, & Herrstedt, 2006). Even with use of antiemetics, CINV, especially nausea, is still a prevalent response to chemotherapy. A recent study by Grote et al. (2006) reported 47% of patients had delayed nausea and 29% had acute nausea during the four days after receiving chemotherapy even with the newest antiemetic regimen of 5-HT₃ receptor antagonist (RA) (palonosetron), NK-₁ RA (aprepitant), and dexamethasone. These patients were being treated with moderately emetogenic chemotherapy. Among breast cancer patients who experienced at least a moderate level of nausea in their prior chemotherapy treatments, the incidences were much higher as 98% experienced delayed nausea, 75% suffered from acute nausea and 58% had delayed vomiting when they received moderate to highly emetogenic chemotherapy with current antiemetics (Dibble et al., 2007).

Current antiemetic guidelines are largely focused on the control of vomiting rather than nausea because there is a better understanding of the mechanisms of chemotherapy-induced vomiting. Incomplete control of CINV, especially nausea, strongly suggests the presence of mechanisms causing CINV which are not well controlled with current antiemetic therapy. In addition, currently recommended antiemetics such as 5-HT₃ RAs and NK-₁ RA are quite expensive, thus a desirable goal is to research more cost-effective modalities for CINV control.

Acupressure has long been used in Traditional Chinese Medicine as one treatment modality for controlling nausea and vomiting. Ezzo et al. (Ezzo et al., 2005) published a meta-analysis result about acupressure effects on acute nausea control. The significant finding of a positive acupressure effect was based on two studies (Dibble, Chapman, Mack, & Shih, 2000; Roscoe et al., 2003) that utilized antiemetics consistent with the American Society of Clinical Oncology guidelines (Gralla et al., 1999). The study by Roscoe et al. (2003) (N=739) that suggested an acupressure band effect in acute nausea control was the basis of the meta-analysis result as the other study by Dibble et al. (2000) only included 17 patients. However, the results presented by Roscoe et al. (2003) differed from the recent acupressure study results obtained by Dibble et al. (2007) which found that digitally applied acupressure was effective in controlling delayed nausea and vomiting, but not in controlling acute nausea. Although each of the acupressure studies suggested acupressure was an effective intervention for CINV, the intervention continues to require further investigation.

The purpose of this review is to evaluate acupressure as an additional intervention in CINV control. The definition and predisposing factors for CINV are described and acupressure theory is presented. Acupressure trials are critically reviewed and directions for future acupressure studies are suggested.

Definition and Predisposing Factors for CINV

CINV is composed of three phases of symptoms associated with chemotherapy. Anticipatory nausea and vomiting is a conditioned response linked to a repeated association of chemotherapy side effects with environmental stimuli that occur within one week prior to the actual administration of chemotherapy (Bender et al., 2002). Acute

CINV is nausea and vomiting occurring within 24 hours after chemotherapy administration (Navari, 2003), and delayed CINV had been arbitrarily defined as beginning more than 24 hours after chemotherapy. With more understanding about the mechanisms of CINV, delayed CINV has been redefined as nausea and vomiting beginning and persisting more than 16 to 24 hours after chemotherapy (Lindley et al., 2005).

Predisposing factors for CINV are an important consideration in intervention studies of CINV, as they could confound the intervention effects. The emetic potential of chemotherapy agents (Hesketh, 1999; Hesketh et al., 1997; Roila et al., 1987; Roila et al., 1985), the female gender (Roila et al., 1987; Roila et al., 1985; Roila et al., 1989) and a younger age (Dibble et al., 2007; Dodd, Onishi, Dibble, & Larson, 1996; Roila et al., 1985; Roila et al., 1989) are well known predisposing factors of CINV. A prior history of motion sickness (Morrow, 1984, 1985), morning sickness during pregnancy (Martin & Diaz-Rubio, 1990), or nausea with stress (Dibble et al., 2007) are all strongly suspected to be predisposing factors of CINV. A history of alcohol use of more than 8.8 ounces of hard liquor/day (D'Acquisto, 1986; Sullivan, Leyden, & Bell, 1983) has been considered as a protective factor of CINV occurrence. However, only a few studies have tested these potential predisposing factors of CINV, thus require further investigation. A history of CINV itself is a considerable factor in CINV development as patients who have had problems with CINV in their earlier chemotherapy treatments typically experience lower response rates to antiemetics in later cycles of emetogenic chemotherapy (Martin, 1996; Roila, 1996; Soukop, 1996).

Acupressure Theory for CINV Control

In Traditional Chinese Medicine (TCM), health is described as a state of balance or harmony within an individual and between the individual and nature (Beal, 1992). Illness can be generalized as disharmony and the target of treatment in TCM is the state of “disharmony,” i.e., any imbalance in the yin and yang and the connecting *Qi* (Kaptchuk, 2002; Liangyue, 1987). Yin and yang are a philosophical conceptualization of both opposite and complementary phenomena within all natural phenomena. TCM applies the yin and yang principles of interconnection and continuous transformation to the human body to explain its physiology and pathology and to guide clinical diagnosis and treatment. *Qi* is the basal energy of the body that flows through the entire body and is the basis for all movement and action (Liangyue, 1987). The channels (meridians) are pathways through which the *Qi* flows throughout the body (Shanghai College of Traditional Medicine, 1981). The traditional channel theory (meridian system) subscribes to the theoretical belief that energy channels (meridians) link internal organs with the externally located acu-points (Shen & Glaspy, 2001). Acu-point stimulation regulates *Qi*, treating both deficient and excessive conditions, as well as regulating the nourishing and protective *Qi*, thereby balancing the yin and yang (Shanghai College of Traditional Medicine, 1981).

The pericardium 6 (P6) is one of the acu-points known to have antiemetic action (Gach, 1990; Liangyue, 1987; Shanghai College of Traditional Medicine, 1981). P6, also known as *Nei-guan*, or the inner gate, is located bilaterally on the pericardial meridian or the anterior surface of the forearm, approximately three finger-widths up from the first wrist crease and between the tendons of the flexor carpi radialis and palmaris longus (Hyde, 1989; Worsley, 1982). Acu-point stimulation through acupressure of P6 can be

conducted by pressing on this point with the fingers or by wearing an elastic wristband with an embedded stud over the point (Ezzo et al., 2005). The acupressure of the points should feel strong but not intolerably painful. In other words, it should hurt in a good way (Beinfield, 1991). The mild discomfort or pain will diminish once the point is firmly held long enough (Gach, 1990), and this is regarded as the “release” of the point.

Methods

Twelve acupressure studies (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Dundee & Yang, 1990a; Dundee, Yang, & McMillan, 1991; Lo, 1998; Melchart, Ihbe-Heffinger, Leps, von Schilling, & Linde, 2006; Meyer, 2001; Molassiotis, Helin, Dabbour, & Hummerston, 2007; Roscoe et al., 2006; Roscoe et al., 2003; Shin, Kim, Shin, & Juon, 2004; Stannard, 1989) that tried to control CINV were found through a database search of PubMed, CINAHL and Digital Dissertations using search terms such as acupressure, P6, nei-guan, neiguan, chemotherapy, nausea and vomiting. A review of the reference list of acupressure studies helped to find three more acupressure studies (Dundee & Yang, 1990b; Noga, 2002; Price, 1992). Among the 15 acupressure studies that investigated its effect in CINV control, 10 controlled clinical trials (one quasi-experimental and nine randomized clinical trials, RCTs) were selected for this review. (S. L. Dibble, Chapman, Mack, & Shih, 2000; S. L. Dibble, Luce, J., Cooper, B.A., Israel, J., Cohen, M., Nussey, B., Rugo, H., 2007; Lo, 1998; Meyer, 2001; Molassiotis, Helin, Dabbour, & Hummerston, 2007; Noga, 2002; Price, 1992; Roscoe et al., 2006; Roscoe et al., 2003; Shin, Kim, Shin, & Juon, 2004). One uncontrolled acupressure bands clinical trial (Stannard, 1989), two uncontrolled clinical trials that combined acupressure with electrical acupuncture (Dundee & Yang, 1990a, 1990b), one uncontrolled trial that

combined acupressure with electrical acupoint stimulation (Dundee, Yang, & McMillan, 1991), and one randomized clinical trial that combined acupressure with acupuncture (Melchart, Ihbe-Heffinger, Leps, von Schilling, & Linde, 2006) were excluded from this review. Each study is reviewed and their design and methodological issues are discussed. Due to the variable methods used in each study, an independent review of each study with a discussion of the identified issues was done instead of combining the results of all the studies in one review and discussion.

Review of Acupressure Studies

Ten controlled acupressure studies were included in this review including one quasi-experimental and nine RCTs. The studies aimed to improve control of CINV by the use of acupressure in addition to prescribed antiemetics. Seven studies selected acupressure band and three studies used finger acupressure as an intervention (Table 1).

Randomized clinical trials with positive acupressure band(s) effect

A cross-over RCT by Price et al. (1992) found lower mean nausea and vomiting scores in the acupressure group ($p < .05$). Patients receiving moderate to highly emetogenic chemotherapy with routine antiemetics over two cycles were randomized to a bilateral P6 acupressure bands (Sea-bands®) group or a sham acupressure bands on both ankles group for one week ($N = 105$). The stratified randomization process was applied to control predisposing factors such as a prior experience with chemotherapy and the emetic potential of the administered chemotherapy agents. Routine antiemetics were administered to both groups, but the use of sub-optimal antiemetics was an issue as 5-HT₃ RAs and NK-1 RA were not used at the time of the study. The effect of acupressure could have been evaluated more precisely if acute and delayed symptom scores were

compared since each phase of CINV is unique. No demographic characteristics were reported and there was a high attrition rate (36%) with complaints about the acupressure bands which limited the generalizability of the results.

Roscoe et al. (2003) tested the acupressure effect on 739 chemotherapy naïve out-patients when continuously wearing an acupressure band (Sea-bands®) at P6 for five days. The patients wore one or two wrist bands. Those who decided to wear one band could wear it on either wrist or alternate wrists. The acupressure group experienced significantly less acute nausea than the control group ($p < .05$) but significance was not obtained for the symptoms of delayed nausea or vomiting. Most of the patients were women (92%) with breast cancer (85%) who received high doses of emetogenic chemotherapy. Stratified randomization was applied for the chemotherapy agent. Antiemetics used for this trial were 5-HT₃ RAs for the acute phase. In the delayed phase, 57% of patients took 5-HT₃ RAs and 61.1% took prochlorperazine. Important predisposing factors for CINV such as prior experience with nausea or vomiting were measured.

However, a positive relationship was found between the patients' expectation of the effectiveness of acupressure and acute and overall nausea control which illustrates the role of expectation in symptom control through acupressure. This in part can be considered as a placebo effect. Among breast cancer patients with doxorubicin treatment ($n = 386$), those women who expected acupressure to be effective reported significantly less severe acute and overall nausea compared to the no expectations or usual care groups ($p \leq .05$). Discriminating true effects from placebo effects of acupressure is an issue. The acupressure group received several minutes of acupressure instruction to be trained in the

use of acupressure band. The additional attention provided to the acupressure group was not controlled in the control group.

In a more recent study, Roscoe et al. (2006) argued that the acupressure effect was more than a placebo through their analysis of 86 breast cancer patients from an earlier study who thought it was very likely that they would have severe nausea and therefore were at high risk for experiencing nausea (Roscoe et al., 2003). Effect of acupressure among patients with low expectations of nausea remains unknown. The proportion of patients in the acupressure band group who reported severe nausea following their chemotherapy treatment was significantly lower and they also had significantly less severe nausea than did the standard care group ($p < .05$). The acupressure band group reported lower average acute nausea score than did the standard care group ($p = .02$). This study also provided contrasting results regarding the suspected placebo effect of the acupressure. There was no significant correlation between expected effectiveness of the band and reports of severe nausea ($p = .56$) or the average severity of acute ($p = .18$) or delayed nausea ($p = .60$). These interesting and somewhat conflicting results provide further support that the acupressure effect on CINV control is not merely an expectation of the acupressure effect (i.e., placebo effect). However, further study is warranted as the number of patients in this analysis of the expectation of acupressure band effect was quite limited ($n = 29$).

A recently reported acupressure bands trial by Molassiotis et al. (2007) supported the effects of acupressure bands in CINV control. The acupressure bands group wore Sea-bands® continuously at P6 bilaterally and pressed the studs for 2-3 minutes every two hours for five days following chemotherapy. The study included 36 female breast

cancer patients receiving moderate to highly emetogenic chemotherapy. Participants received 5-HT₃ RAs and dexamethasone in the acute phase and various antiemetics in the delayed phase. The control group received the usual care with chemotherapy, served as a waitlist group, and was told that they would receive the acupressure instructions and be given the wristbands to use for their next cycle of chemotherapy. One patient who had used acupressure bands in the past was randomized to the control group. This might have influenced the evaluation of the CINV experience without acupressure bands as the patient could have evaluated the CINV in comparison to the experience with acupressure bands. Additional attention provided to the acupressure group was not controlled. Predisposing factors such as age, emetogenic potential of chemotherapy, antiemetics, and history of Nausea and vomiting were considered in the study design. The Rhodes Index of Nausea, Vomiting and Retching (INVR) (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984) was revised by the researchers and used to measure CINV.

The INVR scores for nausea experience, nausea, vomiting occurrence and distress were all significantly lower in the P6 acupressure bands group for five days after chemotherapy (all $p < .05$). It is of interest that the day 3 levels of nausea and vomiting were similar to those experienced by the control group. No post-hoc analysis was conducted, so it is difficult to evaluate the significance of the daily differences and phase specific effects of the acupressure bands. Thirty six patients were included in this study whereas fifty patients were required to achieve a power of 80% at an alpha of .05. A high attrition rate (34%) was also an issue. More patients in the P6 group did not return questionnaires. One participant removed the bands because they were too tight and left

marks for a few days, which suggests another issue to be considered when using the acupressure bands (Table 2).

Randomized clinical trials with negative acupressure band(s) effect

While there are studies that suggested there was a positive effect with the use of acupressure band in CINV control, others reported negative results. A study by Lo (1998) failed to find an effect among Taiwanese children receiving chemotherapy who continuously wore bilateral, size adjustable, velcro acupressure bands (Bio-bands®) at P6. This cross-over study covering two cycles of moderate to highly emetogenic chemotherapy with standard antiemetics included a sham control group with Bio-bands® which lacked the pressing stud. The children were instructed to wear the bands for two hours before and up to three days after chemotherapy, except when bathing (a total of 74 hours). Most had acute lymphoblastic leukemia ($n = 10$), and were recruited from one hospital which could limit generalizability. The sample size ($N = 16$) was less than initially estimated ($N = 34$) and only a few CINV episodes were reported. Factors known to be related to CINV, including gender, the emetic potential of chemotherapy, a history of motion sickness, and a history of CINV were controlled by the study design using a stratified random assignment, which is considered difficult with such a small sample size. It was difficult to evaluate for any phase specific effects of the acupressure because some patients received chemotherapy on days two or three. The Rhodes Index of Nausea and Vomiting, version 2, (Rhodes, Watson, & Johnson, 1984; Rhodes, Watson, Johnson, Madsen, & Beck, 1987) was modified to assess nausea and vomiting responses of the children and parents, who were a surrogate group. The parents' responses showed a moderate to high correlation of the responses from the children. The wording of “feel

distress” was changed into “bothered”. Whether the wording correctly reflected the feeling of distress, as measured by this tool, will need further study. Issues about the acupressure band incurred by the researcher included the tightness of the band, the position of the band, and the level of pressure. It is possible that the provided Bio-bands® were not tight enough to provide enough pressure to exert an antiemetic effect. Band may have slipped out of the correct position. Because few symptoms were reported, it is also possible that Bio-bands® and sham band both had an effect on CINV control, or that the provided standard antiemetics were quite beneficial and thus the acupressure had no additional effect. This is the only trial that applied acupressure to children for CINV control. It is difficult to evaluate if young age had any influence on acupressure effect in CINV control.

Another acupressure band RCT by Meyer (2001) also failed to support the effect of acupressure in the control of CINV ($N = 25$). The intervention was for the patients to continuously wear the Bio-bands® at the P6 site of the dominant hand for five days, and to apply five minutes of pressure when symptoms occurred. The sham group wore the band without a stud and pressed on the posterior wrist. Participants received moderate to highly emetogenic chemotherapy and most patients were breast cancer patients ($n = 21$). Antiemetics included 5-HT₃ RAs and dexamethasone in the acute phase and prochlorperazine or ondansetron in the delayed phase. Nausea and vomiting were measured by the INVR (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984). The INVR scores were low and no significant difference was found between the groups’ mean scores for each item and the symptom scores of the INVR. No statistical analyses were conducted to evaluate changes over time, thus losing a significant benefit for

longitudinal data. Predisposing factors for CINV were well controlled, including age, gender, emetic potential of chemotherapy agents, the use of antiemetics, a history of nausea and vomiting, and a history of heavy alcohol use. Other possible confounders were controlled by the study design, such as excluding patients with bilateral lymphedema and providing acupressure band according to the size of the patient's wrist. It is uncertain if wearing the band around a wrist itself could exert any acupressure effect even without pressing P6 with stud or if provided antiemetics were enough to control CINV in this group of patients. Every patient completed the study and all but two patients wore the band continuously. However, as this study originally aimed to include 60 patients, further patient enrollment was required to achieve enough power to determine a potential difference.

An acupressure bands trial by Noga et al. (2002) involving 120 patients with hematologic malignancies failed to show efficacy for the acupressure. The effect of continuous, bilateral wearing of Bio-bands® at P6 versus an erroneous point for 24 hours after chemotherapy was compared. The sham point was at the posterior wrist. Patients received highly emetogenic chemotherapy and antiemetics including ondansetron and dexamethasone. Some patients received total body irradiation, possibly increasing nausea and vomiting symptoms. The P6 acupressure group had significantly more frequency, duration, and distress of nausea, and a higher nausea subtotal and total INVR score (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984). These patients took significantly more additional antiemetics (all $p < .05$). Why the acupressure group had more nausea and took more additional antiemetics such as lorazepam and prochlorperazine was not explained by the difference of age, gender, chemotherapy regimen, diagnosis, or

anticipatory nausea and vomiting. Other unmeasured predisposing factors and noncompliance of P6 acupressure might have caused more CINV in the P6 acupressure group. It may also be questioned if either the bands did not exert a true acupressure effect, considering reported problems of band slippage from other trials, or if the sham point had any influence in CINV control. It is difficult to evaluate the influence of the cancer type related to the acupressure effect as this study only included patients with hematologic malignancies (Table 3).

Quasi-experimental trial with positive finger acupressure effect

Shin et al. (2004) conducted a five day finger acupressure study with Korean stomach cancer patients who were receiving the first cycle of highly emetogenic chemotherapy. P6 acupressure was performed for five minutes at least three times a day before chemotherapy, and at meal times or based on patient need after chemotherapy ($N = 40$). This non-randomized clinical trial assigned the first 20 patients to the control group and the next 20 to the intervention group. Antiemetics given to the patients were metoclopramide and ondansetron, which are sub-optimal for highly emetogenic chemotherapy. Predisposing factors such as a history of previous nausea and vomiting was not controlled for. Nausea and vomiting was measured by the INVR (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984) and a 0-10 numeric rating scale. The researchers compared daily scores, as well as average scores for each outcome. Data would have been more meaningful if the evaluation had been according to the phases of CINV (i.e., acute and delayed). Although all three average scores of severity, duration, and frequency of nausea and vomiting were significantly different between the acupressure and control groups ($p < .01$), daily comparisons revealed that the most

significantly different effects were demonstrated on days 2-5 for severity, and days 3-5 for duration and frequency measures ($p < .05$). Only duration ($p < .01$) and frequency ($p = .03$) of nausea and vomiting were significantly changed over time in the acupressure group. However, the sample was from one hospital, without randomization, sub-optimal antiemetic use and no control done for predisposing factors which weakened the results of the study. Additional attention provided to the acupressure group was also an issue.

Randomized clinical trials with positive finger acupressure effect

Dibble et al. (2000) conducted a randomized controlled trial with bilateral finger acupressure at P6 and ST36 versus the usual care. ST36 is also known to have an antiemetic effect and is located bilaterally on the stomach meridian approximately four finger-widths below the knee and one finger width lateral to the tibia (Gach, 1990). Finger acupressure of at most three minutes or until the point released was conducted by the patients each morning before and after chemotherapy, and as needed whenever nausea occurred. The effect of acupressure is difficult to differentiate as solely an effect of P6 acupressure, although ST36 was reported as being rarely used by participants in this trial because of difficulties reaching it.

Eight breast cancer patients conducted finger acupressure over one cycle of moderate to highly emetogenic chemotherapy ($N=17$). All received usual and routine antiemetic therapy. Nausea was measured by the three nausea items of the INVR (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984) and the 0-10 Numeric Rating Scale (NRS) of nausea intensity. Significantly fewer nausea experiences over 10 days were noted in the acupressure group ($p < .01$), and a significant daily difference was noted on seven of the 10 days with a lower INVR nausea score in the acupressure group

($p < .05$). Nausea intensity measured by the NRS was also significantly less in the acupressure group ($p < .04$), however a significant daily difference was noted only on day two ($p < .05$). The acupressure group received about five minutes of acupressure instruction which could be interpreted as additional attention given to patients which could then possibly have confound the study results.

Dibble et al. (2007) conducted the most recent finger acupressure study that applied both sham and no-intervention control groups to distinguish the true effect of acupressure. This three-arm RCT included 160 female breast cancer patients who had at least moderate nausea in a previous chemotherapy cycle. Patients in this study applied finger acupressure at P6 every morning to both arms for at the most three minutes each or until the point released, and additional acupressure to one arm as needed during the day. In comparison to prior finger acupressure studies, this acupressure intervention clearly instructed patients to use both arms in the morning and one arm for additional acupressure. The sham group applied acupressure to SI3, a point on the ulnar edge of the hand, approximately halfway along the fifth metacarpal bone, which is considered to have no effect but is close to P6 (Worsley, 1982). Both acupressure groups received the usual care with chemotherapy. The “no-intervention control group” only received the usual care. Additional attention provided to the intervention groups was not controlled by the study design.

The acupressure was conducted over one cycle of moderate to highly emetogenic chemotherapy. All patients received prescribed concurrent antiemetics. Three nausea items (RIN), one vomiting item from the INVR (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984), and the NRS were used to measure CINV for about 21 days.

No difference was found in all the measures of acute CINV among the different intervention groups. A decline of delayed vomiting was significantly greater in the P6 group than in the SI3 placebo group ($p < .01$) and the no-intervention control group ($p < .01$). P6 acupressure in younger women (age < 55) had a significantly steeper decline effect on delayed nausea than for those in the placebo (RIN, $p < .01$ & NRS, $p = .03$) and the no-intervention control group (RIN, $p < .01$ & NRS, $p < .01$). Some issues with finger acupressure identified in this study suggest the need for an improvement in the procedure, as some participants had difficulty finding the points consistently, and two participants had fingernails that were too long which interfered with doing the acupressure correctly (Table 4).

Discussion

Four studies supported the effect of acupressure band in CINV control, especially its effectiveness in decreasing mean nausea and vomiting scores over 7 days (Price, 1992), acute nausea control (Roscoe et al., 2006; Roscoe et al., 2003) and overall nausea and vomiting control (Molassiotis, Helin, Dabbour, & Hummerston, 2007). The studies by Roscoe et al. (2003) and Roscoe et al. (2006) were analyzed from the same data set, and thus total patients in these positive acupressure band trials were limited to three trials with incongruent results. Clarification is required as to whether or not the pressure applied by wearing the band is enough to affect the P6 point, if the stud is necessary to exert additional pressure, and if additional pressure applied by using the hand to press stud provides more control than the continuous application of pressure by wearing the band with stud. Acupressure band RCTs that yielded negative results had design and

methodological issues such as a small sample size, no true control group, and a concern about the sham acupressure band having a possible antiemetic effect.

One quasi-experimental and two randomized controlled finger acupressure studies all yielded positive results in controlling CINV. The intervention was self-administering acupressure for 3-5 minutes (or until point release) and additional finger acupressure as needed. Adherence could be an issue. Two studies did not have a sham control group and thus it was difficult to differentiate the effect of acupressure from placebo therapy, although the results suggested that acupressure was effective in CINV control without discriminating between the phases of CINV (Dibble, Chapman, Mack, & Shih, 2000; Shin, Kim, Shin, & Juon, 2004). Dibble et al. (2007) conducted a three-arm RCT that applied both a sham and a no-intervention control group, making it possible to differentiate a true acupressure effect from the placebo effect in each phase of CINV. The significant decline of delayed nausea and vomiting was noted in the true acupressure group, especially for women under 55 years of age. This finding conflicts with the result of the acupressure band study (Roscoe et al., 2006; Roscoe et al., 2003) which suggested an efficacious response in acute nausea control. The most methodologically convincing three-arm design study (Dibble et al., 2007) strongly suggested finger acupressure as an effective modality in delayed nausea and vomiting control. However, the finger acupressure study has been limited to female breast cancer patients who received moderate to highly emetogenic chemotherapy and also had at least moderate nausea in previous chemotherapy. Further study is clearly required to draw more confident conclusions about the effect of acupressure on CINV control.

Several issues need to be addressed in the studies of acupressure for CINV control. First, the researcher must consider the unique features of CINV. Distinguishing the phases of the symptoms such as acute versus delayed, are required in the measurement as well as in the analysis portions of further investigations. Most acupressure studies investigated its effect during the three to five days after chemotherapy. However, the period of acupressure intervention needs to be matched with the trajectory of CINV as it remains even 10 days after chemotherapy (Dibble, Casey, Nussey, Israel, & Luce, 2004; Dibble et al., 2007; J. Lee, Dibble, Pickett, & Luce, 2005). Predisposing factors for CINV need to be controlled by the study design. With a large sample, stratified random assignment of patients from either a highly or moderately emetogenic chemotherapy group will provide an opportunity to explore the scope of the acupressure effect. Age, gender, history of nausea and vomiting, and the use of alcohol have been considered important predisposing factors for CINV, however, further studies are required to document these factors. These factors need to be measured, assessed for balance between the comparison groups, and evaluated for their influence on the outcomes.

The goal of acupressure research is to provide an additional CINV control with the use of standard antiemetics, and thus the use of antiemetics needs to be controlled. Although the restriction of antiemetics to specific agents is considered important, it is not crucial. Early acupressure studies before the widespread use of 5-HT₃ RAs had problems of suboptimal antiemetic control which made the interpretation of the acupressure effect difficult. In the cases where acupressure shared the mechanism of CINV control with currently recommended antiemetics and the effect of antiemetics were much stronger than the effect of acupressure, the proposed effect of acupressure in older studies may be

difficult to achieve with current antiemetic therapy. However, issues of antiemetic control in recent trials are different. With the widespread use of 5-HT₃ RAs and the inclusion of NK-1 RA in current guidelines, the current practice of antiemetic prescription could reflect recommendations from the guidelines as well as an inevitable gap between the suggested guidelines and actual practice which is affected by issues of cost. Fifty-five different pharmaceutical regimens for delayed CINV control among 160 women in the Dibble et al. (2007) study clearly illustrate this phenomenon. A study of acupuncture with currently used antiemetics is considered acceptable; however, absolute control of antiemetic use would provide clearer data about an additional effect of acupuncture.

Other possible mechanisms of CINV need to be considered. Dibble et al. (2007) reported that baseline anxiety was significantly related to the intensity of delayed nausea for the first four days ($p < .03$). Expectation is one route of nausea development (Hickok, Roscoe, & Morrow, 2001; Montgomery et al., 1998; Watson, Meyer, Thomson, & Osofsky, 1998), and thus it will be meaningful to measure patients' expectations of symptom development and to compare groups of high and low expectancy. Measures of expectation of the treatment effect will help to discriminate the placebo effect from true acupuncture effect, as was done by Roscoe et al. (2003) and Roscoe et al. (2006)

Studies have been primarily conducted in Caucasian women with breast cancer (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Meyer, 2001; Roscoe et al., 2006; Roscoe et al., 2003). Including diverse ethnic groups of patients of both genders who are receiving specified emetogenic categories of chemotherapy agents will help understanding the influence of gender on the effect of acupuncture among diverse ethnic groups. Some studies only included chemotherapy-naïve patients (Meyer, 2001;

Molassiotis, Helin, Dabbour, & Hummerston, 2007; Roscoe et al., 2006; Roscoe et al., 2003; Shin, Kim, Shin, & Juon, 2004), whereas one study only included patients who had certain level of CINV during previous chemotherapy (Dibble et al., 2007).

Comprehensive evaluation of the acupressure effect could be done by including diverse groups of patients including their experiences with CINV.

Second, the researcher must plan for acupressure interventions. Acupressure band and finger acupressure have been studied, and both modalities have implied that it is efficacious. It is important to select a modality with evidence of both efficacy and fewer adverse events for future trials. Issues with the use of acupressure band include the slippage or misplacement of band. Some patients in the study by Price et al. (1992) complained that the bands were excessively tight, irritating, and cosmetically unacceptable. Molassiotis et al. (2007) also reported complaints of tightness. Dibble et al. (2007) reported problems with finger acupressure, such as fingernail interference and difficulty with finding the point consistently. The costs of each intervention are comparable as finger acupressure costs nothing and acupressure bands costs about \$10 each. Reported adverse events and the cost of finger acupressure and acupressure band are comparable, but provides only a little more support for using finger acupressure in future trials. However, no direct comparison of the effect of finger acupressure versus acupressure band has been conducted in the same study, and this needs to occur.

The number of arms used to apply acupressure is also a question. Some studies used both arms for acupressure application while other chose only the dominant arm. Use of the dominant arm for acupressure trial was suggested by Dundee et al. (1988) who explored 189 patients treated with chemotherapy and found that right-handed patients

received a significantly larger benefit from acupuncture than did 19 left-handed patients (Dundee, Fitzpatrick, Ghaly, & Patterson, 1988). In contrast, others recommended the use of both arms. Left- and right-sided acu-points are interrelated, thus selecting both sides could augment the therapeutic effect (Lee & Cheung, 1978). The same point on opposite body sites may react differently to the same acupuncture stimuli, and the use of both arms provides an opportunity to compensate for those differences with acu-point stimulation (Shanghai College of Traditional Medicine, 1981). Utilizing both arms for acupressure intervention fits better with the philosophy of traditional Chinese medicine that tries to balance the *Qi* of patients, which is better achieved through customized augmentation or compensation. Acupressure trials other than Meyer (2001) Applied acupressure to both arms or allowed flexibility in the arm selection. All positive study results of finger acupressure were achieved using both arms. Philosophical underpinnings and experience with acupressure trials support the use of bilateral rather than unilateral acupressure in CINV control.

Acupressure band was applied continuously on one or both arms, and some patients were instructed to press the stud every two hours for 2-3 or five minutes in two studies, or to press the stud for five minutes when nausea occurred in the other study. Finger acupressure was applied to a point for 3-5 minutes (or until release) on one or both arms. Prescribed doses of finger acupressure ranged from once to three times daily, but all allowed for additional acupressure when needed so actual doses were tailored to the needs of the patients. It is considered efficient to allow the intervention to be tailored to patients' antiemetic needs. Dundee (1990) also suggested that acupressure frequency needs to be more often than when needed, including additional times as a set schedule

and considering the difference between inpatients (who are prompted by nursing or medical staff) and outpatients (who lack these health care provider prompts). Patients need to receive or be instructed on how to perform acupressure on a regular basis, and a requirement that additional acupressure interventions is allowed should always be included to meet the individual needs of the patients. Regular doses of finger acupressure are also recommended for prevention purposes. Duration of each acupressure session needs further consideration, as the goal of pressing the point is to obtain the release point. However, the sensation of release could be considered difficult for patients to perceive, so providing an actual time for intervention would facilitate adherence. Three-minute finger acupressure, once daily with additional acupressure as needed, would be the optimal intervention for future acupressure research because both three-minute, once daily and five-minute, three times daily trials have succeeded in achieving positive effects.

Finally, the study design is an important consideration in evaluating the effect of acupressure in CINV control. Initial acupressure trials included heterogeneous samples, making it difficult to interpret treatment effects for certain groups of patients. However, in Lo's trial (1998) which tested acupressure bands to children, and in Noga's trial (2002) which tested acupressure only on hematological malignancy patients, it was also difficult to conclude if the nil effect originated from intervention inefficacy or from the sample or treatment differences because the efficacy of the acupressure was not established at the time of the study. Once the efficacy of acupressure is established through large RCTs in one sub-population such as breast cancer patients, then acupressure research could be

expanded to other sub-populations of interest such as children, men, and other types of cancer groups who receive different levels of emetogenic chemotherapy.

Use of sham control is an important consideration in acupressure research. Dibble et al. (2007) suggested no further need to apply a sham group in acupressure studies, as the effect of acupressure in delayed CINV control in the younger age group was significant. This has already been suggested by Dundee (1988) as dummy point acupuncture yielded no benefit. However, without a sham control group, it is still difficult to determine whether the achieved acupressure effect is a true effect or a placebo effect. The RCTs with a sham control group and without a true control group had limitations for interpreting the results once no significant differences were found. The benefit of discriminating a true effect from the placebo and control groups strongly suggests the need of three-arm design in further acupressure trials.

Conclusion

This review concludes that the effect of acupressure is strongly suggestive but is still not conclusive. The effect of acupressure band was contrasted study by study. Finger acupressure trials all supported the positive effect of acupressure in CINV control. Differences in acupressure modality, emetic potential of chemotherapy agents, antiemetic use and sample characteristics make comparisons between existing research studies difficult. Suggestive effects of acupressure, cost-effectiveness, and non-invasiveness should urge researchers to further investigate its efficacy.

The consideration of issues incurred from this review will benefit planning for future research. The next step would be a three-arm, finger acupressure trial among patients with breast and other cancers who receive moderate to highly emetogenic

chemotherapy with standard antiemetics. Acupressure could be strongly recommended as an effective non-pharmacologic adjuvant intervention for CINV control if its positive effects are reproduced in future acupressure trials

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Table 1. Acupressure Studies

	Acupressure band(s)	Finger acupressure
Quasi-experimental trial with Positive Result		<ul style="list-style-type: none"> Shin et al. (2004): P6, 5 min * 3/day + PRN for 5 days
RCT with Positive Result	<ul style="list-style-type: none"> Price et al. (1992): continuous wearing of Sea-bands® for 1 week Roscoe et al. (2003) & Roscoe et al. (2006): continuous wearing of Sea-bands® for 5 days Molassiotis et al. (2007): continuous wearing of Sea-bands® for 5 days + press the stud 2-3 min every 2 hrs 	<ul style="list-style-type: none"> Dibble et al. (2000): P6 + ST36, 3min * both arm /each morning + PRN over 1 cycle Dibble et al. (2007): P6, 3min * both arm /each morning + PRN at one arm over 1 cycle
RCT with Negative Result	<ul style="list-style-type: none"> Lo (1998): continuous wearing of Bio-bands® for 74 hrs Meyer (2001): continuous wearing of a Bio-band® (dominant hand) for 5 days + 5 min pressure when nausea occurs Noga et al. (2002): continuous wearing of Bio-bands® for 24 hrs 	

Table 2. Summary of Acupressure Band(s) Studies of Positive CINV control

Study	Design	Sample	Emetic potential/ Antiemetics	Measurement	Intervention	Findings	Limitations
Price et al. (1992)	Cross-over design (2 cycles of CTx) Stratified by prior experience and emetic potential of CTx	N=105 51% received HEC	MEC/HEC Routine antiemetics	Diary record of nausea, vomiting, mood, anxiety and overall condition	P6 vs. sham point at ankle acupressure by acupressure bands	Significantly lower average scores for nausea, vomiting and overall condition but not anxiety (p<.05)	No demographic data Suboptimal antiemetic use No analysis about CINV change over time High attrition rate (n=38)
Roscoe et al. (2003)	3-arm RCT; P6 acupressure band, acu stimulation band, usual care Stratified randomization by CTx agent	N=739 Chemo-naive out-patients/ 85% breast Ca/ 88% Caucasian	MEC/HEC; Cisplatin, Doxorubicin 5-HT ₃ RA for acute phase (Dexa or other corticosteroids allowed) 56.7% took 5-HT ₃ , 61.1% took prochlorperazine in delayed phase	Diary: Severity of nausea (7 point scale), number of vomiting episodes 4 times a day Expected efficacy of the wrist band(s) with 5 point scale	P6 acupressure band wear continuously for 5 days (could wear one or two, and the wearing flexibility allowed)	Acupressure band group experienced less acute nausea than control (p<.05) Patients who used acupressure band and expected them to be effective (n=386 breast ca pt) had less severe acute nausea, overall nausea, then who did not expect or no band group (p≤.05) and significantly took less antiemetic meds in delayed phase than not expecting group (p<.05)	Question about placebo effect Additional attention not controlled

Table 2. Summary of Acupressure Studies of Positive CINV control (Cont.)

Study	Design	Sample	Emetic potential/ Antiemetics	Measurement	Intervention	Findings	Limitations
Roscoe et al. (2006)	3 arm RCT; P6 acupressure band (n=29), acu stimulation band (n=26), usual care (n=31)	N=86 Chemo-naïve Female breast cancer pts. (who expected severe nausea)/ 91% white	MEC/HEC; Doxorubicin based CTx	Expected efficacy of the wristband for nausea control (5 point scale), Expected nausea (5 point scale) Nausea severity measured four times daily for 5 days (7 point scale)	P6 acupressure band wear continuously for 5 days (could wear one or two, and the wearing flexibility allowed)	The proportion of patients in the acupressure band group who reported severe nausea following their chemotherapy treatment was less (41%) and had significantly less severe nausea than that of the standard care group, and acustimulation group (p<.05) Acupressure band group reported lower average acute nausea (p=.02) No significant correlation between expected effectiveness of acupressure band and reports of severe nausea (p=.56) or average severity of acute or delayed nausea (p=.18, p=.60)	Small sample size
Molassiotis, Helin, Dabbour, & Hummerston. (2007)	RCT; P6 acupressure bands vs. usual care	N=36 Chemo-naïve Breast cancer Pts/ Mean age=50	MEC/HEC; Doxorubicin + cyclophosphamide (n=15)/ Epirubicin + CMF(n=6) Acute phase; 5-HT ₃ RA + dexamethasone Delayed phase; vary	Daily log: Revised INVR	Bilateral acupressure bands at P6 * 5 days + additional pressure for 2-3 min every 2h	All INVR symptom scores were significantly lower in the P6 group compared to the control group (p<.05) except for vomiting experience Day 3 had similar levels of INVR scores	N=50 required for power 34% attrition Additional attention not controlled Question about placebo effect Control group served as a wait list group could have influenced subjective report about symptom Even one patient had prior experience of using acupressure band included in the control group No statistical analysis about change over time No post-hoc analysis about daily difference

CTx: Chemotherapy

MEC: Moderately Emetogenic Chemotherapy

HEC: Highly Emetogenic Chemotherapy

CEF: cyclophosphamide + epirubicin + 5-FU

CMF: cyclophosphamide + methotrexate + 5-FU

Table 3. Summary of Acupressure Band(s) Studies of Negative CINV Control

Study	Design	Sample	Emetic potential/ Antiemetics	Measurement	Intervention	Findings	Limitations
Lo (1998)	Cross-over; P6 Acupressur ebands vs. Sham bands without stud	N=16 (n=12; boys) Mean age=13 lymphoblastic leukemia (n=10)	MEC/HEC standard antiemetics	Adapted INVR child and parent version every 12 hrs, 0-10 NV VAS scale every 12 hrs, NCI-NV every 24 hrs	Wear acupressure bands at P6 2 hrs before CTx and continuously for 72hrs	No acupressure bands or course effect	Small sample size (smaller than estimated size, i.e. power issue) Patients from one hospital No true control group Multiple day CTx Measurement issue Question about acupressure effect of the sham bands
Meyer (2001)	RCT; P6 Acupressur eband vs. Sham band without stud	N=25 Chemo native Breast cancer pts (n=21)	MEC/HEC standard antiemetics	Daily log; the INVR	Wear a P6 acupressure band continuously at dominant arm for 5 days and press stud when symptom occurs for 5 minutes vs. Sham band and press posterior wrist when symptom occurs. At 30 min before CTx and continued 4 days after CTx	No significant difference between groups Low INVR scores in both groups	Small sample size (smaller than estimated size, i.e. power issue) No true control group No statistical analysis about change over time Question about acupressure effect of the sham band
Noga et al. (2002)	RCT; P6 Acupressur ebands vs. Sham bands with stud	N=120 (70 male + 50 female) Hematologic malignancy pts/ Mean age=48/ 83% Caucasian	HEC Antiemetics according to algorithm and standard orders	Modified INVR	P6 point acupressure bands vs. sham bands at posterior wrist for 24 hrs	P6 acupressure bands group had more nausea frequency, duration and distress, higher nausea subtotal score, and total INVR score (p<.05) P6 acupressure bands group took more additional antiemetics (p<.05)	No true control group Only patients with hematologic malignancy Some pts received RTx

Table 4. Summary of Finger Acupressure Studies of Positive CINV control

Study	Design	Sample	Emetic potential/ Antiemetics	Measurement	Intervention	Findings	Limitations
Shin et al. (2004)	Quasi-experimental trial; P6 finger acupressure vs. usual care	N=40 Chemo-naïve Korean Stomach Ca pts/ Mean age=50/ 28 male, 12 female	HEC; Cisplatin + 5-FU Antiemetics; metoclopramide and ondansetron	Daily log: Korean version of INVR, 0-10 numeric rating scale	P6 finger acupressure for 5 mins * at least 3 times a day before CTx and meal times or prn after CTx	Less severe NV in P6 group on average of 5 days (p<.01), only significant on day 3 and 4 Less average duration of NV in P6 group (p<.01), only significant at day 2 to 5 Less frequent NV in P6 group in average (p<.01), only significant from day 3 to 5 Significant difference in change over time in P6 group in duration and frequency of NV (p<.05)	No randomization Sub-optimal antiemetics Uncontrolled predisposing factors such as history of NV No phase specific analysis Participants from one hospital
Dibble et al. (2000)	RCT over single cycle; P6 finger acupressure vs. usual care	N=17 Female Breast Cancer Pt/ Mean age= 50/ 59% Caucasia n	MEC/HEC; Doxorubicin or CMF Usual antiemetics	Daily log: 3 nausea items from the INVR (0-12), nausea intensity (0-10)	P6 and ST36 bilateral finger acupressure for maximum of 3 minutes or until the point released, each morning and prn	Significantly less nausea experience in acupressure group (p<.01), significant daily difference noted 7/10 days. Less nausea intensity (p<.04), significant daily difference only at day 2 Rarely used ST36 because reaching was difficult, especially in public	Small sample size Only female breast cancer patients Question about placebo effect Difference in attention (approximately 5 min more in acupressure group) Confounded by the ST36 acupressure intervention

Table 4. Summary of Acupressure Studies of CINV Positive Control (Cont.)

Study	Design	Sample	Emetic potential/ Antiemetics	Measurement	Intervention	Findings	Limitations
Dibble et al. (2007)	3 arm RCT over one cycle; P6 finger acupressure, placebo, P6 finger acupressure, no intervention	N=160 Breast cancer pts who had at least moderate nausea in prior CTx/ Mean age=49/74% Caucasian	MEC/HEC; Anthra-cycline+ cyclo-phosphamid e (76%) Prescribed antiemetics	Daily log for app. 21 days until their next cycle of CTx (3 nausea items (RIN, 0-12) + 1 vomiting item (0-4) from the INVR, nausea intensity numeric rating scale (NRS, 0-10)	P6 finger acupressure each morning; thumb pressure at P6, at most 3 mins, to both P6 points + one point prn vs. placebo finger acupressure on S13 vs. no intervention	42% had delayed emesis Decline in delayed emesis was significantly greater in P6 group than placebo (p<.01) or no intervention (p<.01) Younger women (< 55 years) reported delayed emesis more frequently immediately following tx and steeper decline (p<.01) 98% had delayed nausea. Reported declines in delayed nausea (RIN, NRS) were greater for P6 group than no intervention group (p<.01) Younger acupressure group (< 55 years) had significantly steeper decline in delayed nausea than placebo or no intervention group (P<.05)	Only female breast cancer patients Additional attention not controlled

Chapter 2.

The Relationship of Chemotherapy-Induced Nausea
to the Frequency of P6 Digital Acupressure

Lee, J., Dibble, S., Dodd, M., Abrams, D, & Burns, B

Will be submitted for Publication

Abstract

Chemotherapy-induced nausea (CIN) was explored in relation to the frequency of P6 digital acupressure among 53 breast cancer patients who had received moderate to highly emetogenic chemotherapy. Data were collected as part of a multi-center, longitudinal, randomized clinical trial. A daily log was used to record CIN and the frequency of acupressure for 11 days after the administration of chemotherapy. A hierarchical generalized linear modeling procedure was used to analyze the data. The mean nausea intensity over 11 days was 2.88 ($SD = 2.83$, $range\ 0-10$) and the participants used acupressure an average of two times per day ($SD = 1.84$, $range\ 0-10$). Nausea intensity was increased by 0.25 points each day from day 1 to 3 (peaked on day 3) ($IRR = 1.25$, $p < 0.01$), and was decreased by 0.37 points each day from day 4 to 11 (after the peak), while holding other variables in the model constant ($IRR = 0.63$, $p < 0.01$). In general, participants with more intense nausea used acupressure more frequently. Those women who used acupressure more frequently on day 4 were the ones who had a 0.52 point higher nausea intensity than those who used acupressure less frequently in the acute phase, while holding other variables in the model constant ($IRR = 1.52$, $p < 0.01$). Those women who used acupressure five or more times, even after the peak of the nausea, experienced the most intense nausea from the first day (acute phase) and their symptom continued to be the highest over 11 days after chemotherapy administration.

Key Words: Breast cancer, chemotherapy, nausea, chemotherapy-induced nausea, P6 digital acupressure, acupressure

Introduction

The American Cancer Society estimated 1,437,180 new cancer patients in 2008 (American Cancer Society, 2008), and 80% of them will receive chemotherapy (Massaro & Lenz, 2005). This indicates more than one million cancer patients are expected to undergo chemotherapy in 2008. Chemotherapy-induced nausea (CIN) is known as the most distressing side effect of chemotherapy (de Boer-Dennert et al., 1997; Griffin et al., 1996; Rhodes & McDaniel, 2001). In the recent study by Molassiotis et al. (Molassiotis et al., 2008), up to 71.4% had acute nausea that occurred within 24 hours after chemotherapy administration (Navari, 2003) and up to 60% experienced delayed nausea which began and persisted more than 16 to 24 hours after chemotherapy (Lindley et al., 2005) when highly emetogenic chemotherapy was administered. With moderately emetogenic chemotherapy, up to 47.4% had acute nausea and up to 61.3% experienced delayed nausea among 102 patients with diverse cancer diagnoses who received routine antiemetics. Even when patients were treated for moderately emetogenic chemotherapy with the newest 5-hydroxytryptamine 3 receptor antagonist (5-HT₃ RA, palonosetron), neurokinin-1 receptor antagonist (NK-1 RA, aprepitant), and dexamethasone, 29% still reported acute nausea and 47% experienced delayed nausea (Grote et al., 2006). Incomplete control of CIN strongly suggests the presence of mechanisms that are not well understood or controlled with current antiemetic therapy. Common adverse effects of 5-HT₃ RAs, such as headache, dizziness, constipation, and diarrhea (Kovac, 2003), and adverse effects of NK-1 RA such as asthenia and fatigue (Dando & Perry, 2004), call for additional interventions for CIN control. Furthermore, currently recommended

antiemetics such as 5-HT₃ RAs and NK-1 RA are quite expensive, thus more cost-effective modalities with less adverse effects for additional CIN control are desirable.

The effect of pericardium 6 (P6, *Nei-guan*) acupressure in CIN control has been supported through six randomized (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Molassiotis, Helin, Dabbour, & Hummerston, 2007; Price, 1992; Roscoe et al., 2006; Roscoe et al., 2003) and one quasi-experimental (Shin, Kim, Shin, & Juon, 2004) clinical trials as well as in one meta-analysis (Ezzo et al., 2005). It is believed in Traditional Chinese Medicine (TCM) that the vital energy of the body, *Qi* resumes its balance when pressing the acupressure point (Liangyue, 1987; Shanghai College of Traditional Medicine, 1981; Stux & Pomeranz, 2003). In the studies of P6 digital acupressure, pressure at P6 was applied for 3 to 5 minutes for 1 to 3 times daily plus additional acupressure as needed per day, for at least 5 days over one cycle of chemotherapy (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Shin, Kim, Shin, & Juon, 2004). The actual frequency of acupressure in the above studies could have ranged from none to several applications per day. It is unknown how frequently patients applied acupressure and whether their experience of CIN had any relationship with the frequency of acupressure.

The purpose of this study is to explore the experience of CIN in relation to the frequency of P6 digital acupressure in a group of breast cancer patients who received moderate to highly emetogenic chemotherapy and applied P6 digital acupressure as an additional intervention for CIN control. The antiemetic therapy ordered for these women to control their CIN was that of the health care providers' choice.

Methods

Design

This study is a secondary data analysis of a multi-center, longitudinal, randomized clinical trial (RCT) that compared differences in chemotherapy-induced nausea and vomiting among three groups of women (P6 digital acupressure, placebo digital acupressure, and usual care) undergoing chemotherapy for breast cancer.

Sample

This study included 53 female breast cancer patients who were randomly assigned to the P6 digital acupressure group in the parent study. Participants were recruited from 10 community clinical oncology programs associated with the University of Texas M.D. Anderson Cancer Center and nine independent sites located throughout the United States. Inclusion criteria included: 1) Women who were receiving cyclophosphamide with or without 5-fluorouracil, doxorubicin with paclitaxel or docetaxel, or 5-fluorouracil, epirubicin, and cyclophosphamide for the treatment of breast cancer. 2) Women who had a nausea intensity score with previous chemotherapy of at least 3 (moderate) on the Morrow Assessment of Nausea and Emesis, which measures the worst nausea. 3) Women who were beginning their second or third cycle of chemotherapy. 4) Women who were able to communicate in English (both verbally and in writing). 5) Women who were willing to participate in the study.

Instruments

A patient information questionnaire was used to collect demographic information and predisposing factors for CIN, including age, gender, and a prior history of nausea such as motion sickness, morning sickness, and nausea with stress. A disease and treatment questionnaire was used to collect medical information including the diagnosis

of breast cancer, chemotherapy regimen, chemotherapy dosages, and antiemetics that were given onsite.

A daily log was used by the participants in the evening to record their CIN and the use of P6 digital acupressure. CIN was measured by a 0-10 nausea intensity numeric rating scale (NRS) and by the 0-12 nausea score from the Rhodes Index of Nausea, Vomiting and Retching (INVR) which has established reliability and validity (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984; Rhodes, Watson, Johnson, Madsen, & Beck, 1987). The NRS had been tested in parallel with the INVR in studies of chemotherapy-induced nausea and vomiting and yielded significant high correlation ($r = 0.75-0.95$) (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Lee, Dibble, Pickett, & Luce, 2005). Acupressure use was measured by the frequency of P6 digital acupressure. In the parent study, participants were instructed to perform digital acupressure for 3 minutes (or until point release) at the P6 points on both arms in the morning, and an additional 3 minutes of acupressure to one arm whenever nausea occurred. The daily logs for the 11 days after chemotherapy were used for the purpose of this study. Participants reported their beliefs on whether they received true acupressure or not at the end of the study.

Analytic approaches

Hierarchical Generalized Linear Model (HGLM) was used to predict changes of CIN in relation to the frequency of P6 digital acupressure over the 11 days following chemotherapy. The association between nausea intensity and the frequency of acupressure was tested by correlation analysis. The influence of known or possible predisposing factors of CIN was also tested through HGLM. Possible predisposing

factors were selected from correlation analysis. Cross-sectional negative binomial regression was used to determine associations of known or possible predisposing factors of CIN to the difference in CIN or acupuncture frequency. Statistical Software SPSS for Windows™ 14.0 (SPSS Inc.) and STATA 10 SE (Stata Corp LP) were used to analyze data.

Results

Demographics

A total of 53 female breast cancer patients with mean age of 49 ($SD = 10.55$, range 27-74) were included in this study. Eighty-one percent of the women were white and 71.7% were married. On average, participants had 14.7 years of education and 41.5% of them were employed. Overall participants were obese with a mean Body Mass Index, BMI of 27.31 ($SD = 5.18$, range 18.98-43.89). Eighty-one percent of them had a diagnosis of ductal carcinoma, and 15% had lobular breast cancer. Forty-nine percent were treated with mastectomy and 47.2% were treated with lumpectomy. Three-quarters of the women underwent nodal dissection (73.6%). Seventy-five percent were treated with anthracycline and cyclophosphamide (AC), 13.2% received 5-fluouracil with AC, and 7.5% received a taxane with AC. Four participants received radiation therapy as a part of their treatment. To evaluate initial control of CIN with antiemetics, the use of antiemetics were compared to the 2008 National Comprehensive Cancer Network (NCCN) antiemetic guidelines (NCCN, 2008). No participant received antiemetics as outlined in the NCCN antiemetic guidelines for highly emetogenic chemotherapy. There were only eight participants who received aprepitant as their antiemetic. When antiemetic use was compared to the NCCN antiemetic guideline for moderately emetogenic

chemotherapy, 71.7% received recommended antiemetics in the acute phase, however, only 26.4% received recommended antiemetics for the delayed phase.

CIN

All 46 participants (87% of the total 53 participants) who provided daily records of CIN and the frequency of P6 digital acupressure experienced some level of nausea during days 1-11. One participant who reported the highest nausea on day 11 was excluded from the analysis as the participant was considered as an outlier. The results from the nausea intensity ratings will be presented in this study as the nausea intensity ratings from NRS were highly correlated with the INVR nausea scores ($r = 0.92, p < .01$) and the results from HGLM analysis corresponded to each other with only a slight difference in the incidence rate ratio (*IRR*).

On average, the participants experienced nausea up to day 8 ($mean = 7.93, SD = 2.68, range 1-11$), and stopped having the symptom from day 9 onward. Participants used antiemetics up to day 6 and stopped using antiemetics from day 7 ($mean = 5.95, SD = 2.83, range 1-11$). The largest proportion of patients stopped using antiemetics on day 5 ($n = 9$). The average nausea intensity rating over 11 days was 2.88 ($SD = 2.83, range 0-10$) and the highest nausea intensity was observed on day 3 ($mean = 4.93, SD = 2.57, range 0-10$). The nausea intensity increased from day 1 to 3 and decreased after that time (Figure 1).

P6 digital acupressure frequency

The average amount of acupressure use in P6 acupressure group over 11 days was two times per day ($mean = 1.9, SD = 1.84, range 0-10$). Participants used acupressure for an average of 7 days after chemotherapy ($mean = 7.37, SD = 3.18, range 1-11$). The most

frequent application of acupressure was on day 3. Throughout the day 3, 12 participants applied acupressure more than five times per day (the largest number of subjects who used more than five times of acupressure during 11 days), 16 participants used acupressure 3-4 times per day, and 10 participants used acupressure 1-2 times per day. Among those women in the P6 acupressure group who answered a question about their beliefs related to acupressure intervention, 73.8% believed that they received true acupressure, whereas 26.2% thought that they had not. There were four participants who did not use any acupressure on day 3: One did not have nausea and did not use any antiemetics. Three women scored their nausea intensity at 3, 5, and 8 and two used antiemetics according to the NCCN antiemetic guideline for moderately emetogenic chemotherapy for the acute phase, but not during the delayed phase. Two of four women believed they were getting real acupressure, one thought she was receiving sham acupressure, and one did not report about her belief (Table 1. for acupressure use over 11 days).

CIN in relation to the P6 digital acupressure frequency

A HGLM analysis suggested that there was a significant change in nausea intensity ratings depending on the time after chemotherapy infusion, while holding other variables in the model constant. There was 0.25 point increase in the nausea intensity ratings (0-10) with each day after chemotherapy from days 1 to 3 ($IRR = 1.25, p = .02$). There was 0.42 point decrease in nausea intensity ratings from days 4 to 11 ($IRR = 0.58, p < .01$). As predicted in the study protocol (participants were instructed to use acupressure whenever nausea occurred), participants who used more acupressure during the acute phase (day1) were the ones who experienced more intense nausea. Those

women who used acupressure more frequently (one more application of acupressure), had a 0.12 point ($IRR = 1.12, p = .01$) higher nausea intensity rating than those women who used acupressure less frequently in the acute phase (day1), while holding other variables constant. The increase in nausea intensity ratings from day 1 to 3 was not depending on the frequency of the acupressure ($IRR = 0.96, p = .20$). The decrease in nausea intensity ratings from day 4 to 11 was dependent on the frequency of the acupressure, when holding other variables in the model constant ($IRR = 1.11, p < .01$). This result suggests that the nausea intensity decreases differently according to the frequency of acupressure from day 4 to 11. However, the pattern of nausea increase during days 1 to 3 was not different according to the frequency of acupressure from day 1 to 3. When the graph was drawn comparing the predicted value of nausea intensity in relation to the acupressure frequency through the HGLM, those women who experienced more intense nausea used more frequent acupressure. A positive association between the nausea intensity and the frequency of acupressure was also found in the correlation analysis ($r = 0.53, p < .01$). A different pattern of nausea intensity changes especially after day 3 was observed among those women who used acupressure more than five times per day (Figure 2).

There was an issue in interpreting the results as the graph line represented the mean nausea intensity of a group of participants who used a certain number of acupressure intervention on a specific day. The group of participants who used a certain acupressure category was different depending on the day after chemotherapy. As the acupressure frequency had made a significant contribution to the change in nausea intensity ratings during days 4 to 11 (after the peak of nausea), acupressure frequency for this period was reviewed. An interesting trend was found in participants who used

acupressure more than five times during the period as they were the ones who used acupressure more than five times on day 4 (illustrated as a solid line). Participants were re-categorized according to the acupressure frequency on day 4. The graph was redrawn to reflect the group of subjects who used different frequencies of acupressure on day 4. Those women who used acupressure more than five times on day 4 had highest nausea intensity over the 11 days. Their peak nausea intensity was different from the other groups (Figure 3). A HGLM analysis with the new categorization of the participants showed significant changes in nausea intensity depending on the length of time after chemotherapy infusion, while holding other variables in the model constant. There was 0.25 point increase in the nausea intensity with each additional day after chemotherapy from days 1 to 3 ($IRR = 1.25, p < .01$). There was also 0.37 point decrease in nausea intensity from days 4 to 11 ($IRR = 0.63, p < .01$). Those women who used acupressure more frequently on day 4 (one level higher in the acupressure frequency category), were the ones who had 0.52 point higher acute nausea intensity than those women who used acupressure less frequently, while holding other variables constant ($IRR = 1.52, p < .01$). However, nausea intensity changes over time were not dependent on the acupressure frequency on day 4. This is interpreted as those women who used more frequent acupressure on day 4 were having higher levels of nausea intensity from the acute phase and continued to experience higher levels of nausea intensity over 11 days. A graphic difference in the peak of nausea intensity observed in Figure 3 was not supported in this HGLM analysis (Figure 4).

The question remained as to whether those women who used acupressure more than five times on day 4 were different from others in their CIN experience. Participants

were re-categorized into two groups (those women who used acupressure more than five times on day 4 vs. others). A HGLM analysis showed significant changes in the nausea intensity ratings depending on the time after the chemotherapy infusion, while holding other variables in the model constant. There was 0.24 point increase in the nausea intensity with each additional day after chemotherapy from days 1 to 3 ($IRR = 1.24, p < .01$). There was also 0.37 point decrease in nausea intensity from days 4 to 11 ($IRR = 0.63, p < .01$). Those women who used acupressure more than 5 times were the ones who had a 0.88 point ($IRR = 1.88, p = .02$) higher acute (Day 1) nausea intensity than those women who used acupressure less frequently, while holding other variables constant. Nausea intensity changes over time were not dependent on the acupressure frequency on day 4. Those women who used acupressure more than five times after the peak of nausea experienced more intense nausea from the acute phase and the symptom intensity stayed higher than others over 11 days (Figure 5). Eighty percent of those women who used acupressure more than five times on day 4 believed that they have received true P6 digital acupressure ($n=4$).

Predisposing factors

A HGLM analysis was conducted regarding known predisposing factors as well as possible predisposing factors for nausea (selected from the correlation analysis) because these factors might have confounded the analysis of nausea intensity and acupressure frequency. As the total sample was limited in size, each possible factor was entered in the HGLM model that analyzed CIN change in relation to the frequency of acupressure. Age and BMI were significant contributing factors to the difference in the nausea intensity in the acute phase although the change was small, when holding other

variables constant. With each year increase in age, there was a 0.03 point decrease in nausea intensity ratings (IRR=0.97, $p<.01$). With each BMI unit increase, there was a 0.04 point decrease in the nausea intensity ratings (IRR=0.96, $p=.03$). Age and BMI were also significantly associated with the nausea intensity ratings when the participants were re-categorized into four groups (IRR=0.97 for age and IRR=0.94 for BMI, both $p<.01$) or two groups (IRR=0.96 for age and IRR=0.95 for BMI, both $p<.01$) according to the frequency of acupressure applied on day 4.

Although the patients with more nausea applied acupressure more frequently in general, the nausea ratings varied among individuals even with the same frequency of acupressure application. Cross-sectional negative binomial regression was conducted to evaluate whether nausea ratings were different in relation to known or possible predisposing factors of nausea when the same frequency of acupressure was applied. Acute phase nausea differences were not explained by any known or possible predisposing factors of CINV when the same frequency of acupressure was used. Delayed phase nausea differences (especially with the patients who used acupressure 3-4 times on day 4) were associated with using antiemetics in the acute phase according to NCCN (NCCN, 2008) guideline for moderately emetogenic chemotherapy. Those women who used antiemetics according to the guideline in the acute phase experienced 0.44 point less intense nausea on day 4 (IRR=0.56, $p=.03$, $n=21$). This supports the importance of initial control of the nausea with antiemetics in the acute phase. However, antiemetic use during the delayed phase was not related to the differences in the nausea intensity according to the guideline. The difference in the frequency of acupressure when

nausea levels were similar was not explained by any known or possible predisposing factors of CINV.

Discussion

This is the first study that reports CIN changes over 11 days in relation to the frequency of P6 digital acupressure. The pattern of nausea intensity changed over time with the peak nausea on day 3 corresponding with the results from the studies with middle aged, mostly white and female breast cancer patients (Dibble, Chapman, Mack, & Shih, 2000; Lee, Dibble, Pickett, & Luce, 2005; Molassiotis, Helin, Dabbour, & Hummerston, 2007). This study proposes that the frequency of acupressure on day 4 had a significant relationship with the nausea intensity in the acute phase and the initial difference in nausea intensity sustained over the 11 days after chemotherapy. Those women who used acupressure more than five times on day 4 experienced the most intense nausea over the entire 11 days.

The influence of acute nausea on delayed nausea has been reported in other studies (Italian Group for Antiemetic Research, 1994, 1997, 2000). In this study, when the frequency of acupressure was similar, those women who used antiemetics according to the NCCN antiemetic guideline in the acute phase experienced less intense nausea on day 4. This further suggests the importance of acute nausea control and the need for concurrent antiemetic use according to the guidelines during the acute phase for better control of delayed nausea. However, delayed phase antiemetic use according to the guideline was not related with the nausea difference on day 4. It is questionable whether the antiemetic guidelines for the delayed phase are less beneficial in controlling delayed

nausea as these guidelines have been more focused on the control of vomiting rather than nausea (Herrstedt, 2008).

This study demonstrated how participants actually applied acupressure after they were given acupressure instructions i.e., applying the mandatory, once daily acupressure and additional acupressure as needed. On average, the participants used acupressure for one more day after they had stopped taking their antiemetics. This suggests a need for acupressure in addition to the given antiemetics during the delayed phase as participants need to control their symptoms through some kind of intervention when antiemetic use is not necessary or when antiemetics are discontinued due to side effects. It is notable that the individual's use of acupressure was variable, although participants with more intense nausea utilized more frequent acupressure in general. On each day after chemotherapy, there were participants who did not use acupressure at all, and there were also participants who used acupressure more frequently than average. Even with a similar level of nausea experience on a certain day, the frequency of acupressure among participants was varied but the difference in acupressure frequency was not explained by known or possible predisposing factors of CIN. Further study is recommended to understand the different needs for acupressure frequency as this finding is from a small number of participants whose nausea level was similar on a certain day. Other uninvestigated factors such as genetic predisposition or TCM diagnosis of the participants according to TCM theory might lend some insights in the use of acupressure for CIN.

Age and BMI were found to be contributing factors to the differences in acute nausea intensity, although further analyses, such as association with acupressure

frequency and delayed phase CIN, were limited by the small sample size. Age is a well known predisposing factor of CIN. It has been reported that younger patients experience more CIN than do older patients (Booth et al., 2007; Dibble et al., 2007; Dodd, Onishi, Dibble, & Larson, 1996; Roila et al., 1985; Roila et al., 1989). In this study, younger participant also experienced a higher intensity of CIN. As the age of participant increased, the intensity of the CIN decreased. The cut-off point for young or old age needs further investigation as studies utilized different cut-off points in comparing age groups (Booth et al., 2007; Dibble et al., 2007; Dodd, Onishi, Dibble, & Larson, 1996; Roila et al., 1985; Roila et al., 1989). This study did not stratify participants into different age groups in analyzing the relationship of age and CIN.

Reports about BMI as a predisposing factor for nausea are not consistent. In this study, participants with lower BMI experienced more intense CIN. In the study that investigated vomiting among patients with metastatic gastrointestinal cancer, lower BMI was related to more vomiting (Farker et al., 2006). Low BMI also has been reported as being associated with more vomiting with pregnancy (Ben-Aroya, Lurie, Segal, Hallak, & Glezerman, 2005) and higher incidence of hyperemesis gravidarum (Matsuo, Ushioda, Nagamatsu, & Kimura, 2007). In contrast, BMI was not a risk factor in the systematic review about BMI related to postoperative nausea and vomiting (Kranke et al., 2001). However, the mechanisms of chemotherapy induced-vomiting, vomiting with pregnancy, or postoperative nausea and vomiting are considered different from that of CIN. It is also unclear whether BMI is associated with CIN in the same pattern as with chemotherapy-induced vomiting, vomiting with pregnancy, or postoperative nausea and vomiting. In the study of delayed CIN among female breast cancer patients, participants with a higher

BMI experienced more severe delayed nausea (Dibble, Isreal, Nussey, Casey, & Luce, 2003). Contrasting results in two CIN studies raises the question of whether BMI is a true predisposing factor of CIN or are some other factors such as chemotherapy dose or the use of antiemetics confounding the relationship. Clearly, the relationship between BMI and CIN needs further investigation in a future study.

It is of interest that most of those women who used acupressure more than five times after the peak of nausea believed they had received true P6 digital acupressure although they experienced the most intense nausea over 11 days in comparison to the others. This finding suggests the benefit of applying acupressure according to the patient's needs. This further supports the acupressure protocol that instructs patients to use acupressure according to their perceived needs. It is questionable whether using other acupressure protocols such as using acupressure only when needed or using more frequent mandatory acupressure and allowing additional acupressure as needed would achieve similar outcomes in controlling CIN. To evaluate the influence of a different frequency of acupressure in achieving control of CIN, a study needs to include different acupressure protocol groups.

It is of interest whether or not acupressure could achieve additional control of CIN when antiemetics that are recommended by NCCN (NCCN, 2008) for highly emetogenic chemotherapy (5-HT₃ RA, NK-1 RA, and dexamethasone in acute phase and NK-1 RA for day 2 to 3, and dexamethasone for day 2 to 4) are used for CIN control with highly emetogenic chemotherapy. No acupressure trials could be located in the literature that used acupressure with a strict control of antiemetics according to the published antiemetic guidelines. Strict control of antiemetic use in acupressure trials will help

understand how much additional benefit could be provided through acupressure. When an antiemetic prescription is controlled and the antiemetic use is tracked, one interesting question is whether additional acupressure could decrease antiemetic use. However, there is still an issue that not all clinicians adhere to the antiemetic guidelines, as well as issue that the antiemetic guidelines are mainly for vomiting control and are less effective in nausea control (Herrstedt, 2008). This study utilized antiemetics of the provider's choice which reflect usual practice; however, there were only 8 participants who received aprepitant as their antiemetic because aprepitant was released toward the end of the study and no participant received antiemetics according to the NCCN antiemetic guideline for highly emetogenic chemotherapy (NCCN, 2008). Further study is required as to evaluate the acupressure effect with current antiemetics since aprepitant is now considered as a standard antiemetic for highly emetogenic chemotherapy.

P6 digital acupressure has been shown to be effective in controlling CIN. The levels of nausea intensity among participants who used various frequencies of acupressure were not identical. This study suggests those women who used more frequent acupressure on day 4 were the ones whose acute nausea was more intense than others. The importance of controlling acute nausea was further emphasized as the initial difference in nausea intensity continued throughout the 11 days after chemotherapy. For further implications of the study findings to the clinical practice, such as improving the care of acute nausea, or identifying patients who are predisposed to require more acupressure or experience more intense nausea, further study regarding the CIN and the frequency of P6 digital acupressure with a large number of participants is strongly recommended.

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Table 1. Acupressure Frequency

Day	Mean	SD	Range
1	2.18	1.53	0-8
2	3.28	2.15	0-10
3	3.32	1.93	0-8
4	2.69	1.73	0-6
5	2.30	1.91	0-9
6	1.80	1.58	0-6
7	1.39	1.41	0-6
8	1.23	1.34	0-4
9	0.88	1.35	0-4
10	0.78	1.21	0-4
11	0.79	1.22	0-4

Figure 1. Predicted Value of Nausea Intensity through HGLM

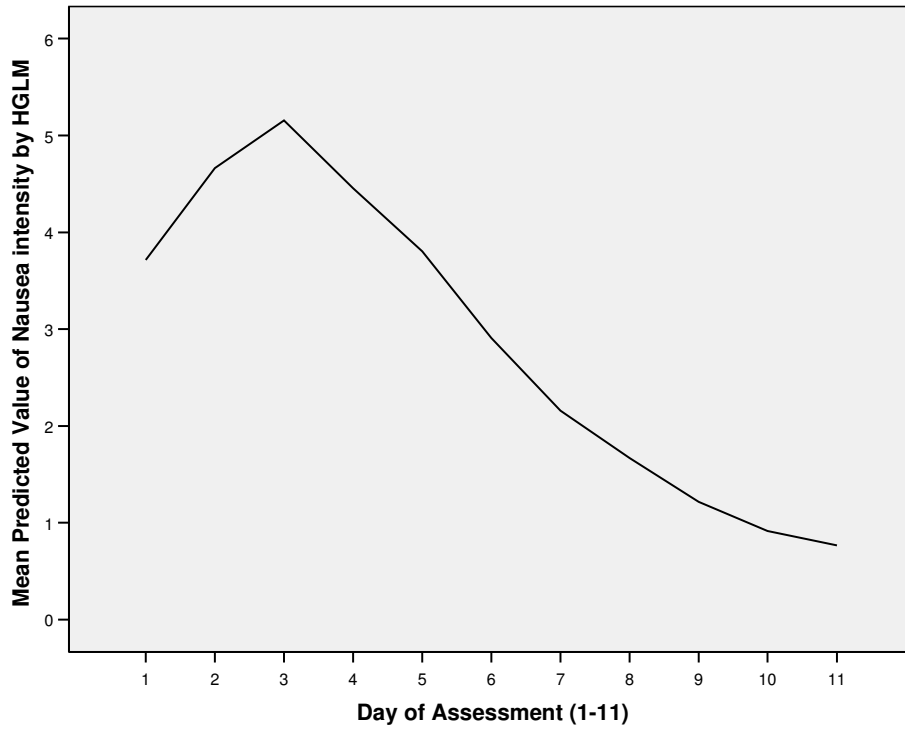


Figure 2. Predicted Value of Nausea Intensity by Four Categories of Acupressure Frequency

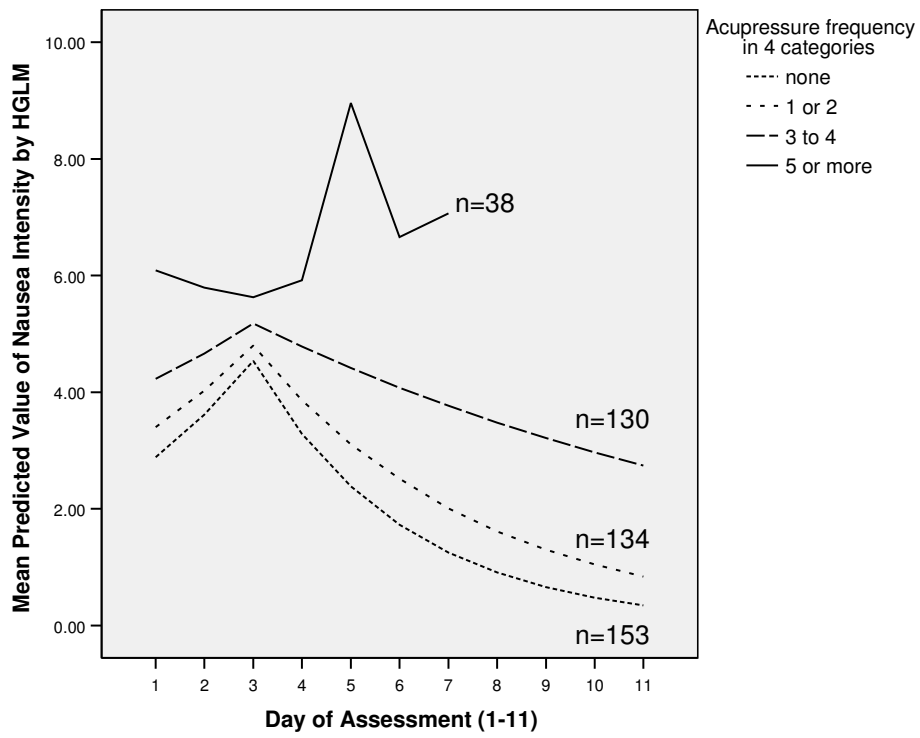


Figure 3. Predicted Value of Nausea Intensity:
 Re-categorized into Four Category Based on Day 4 Acupressure Frequency

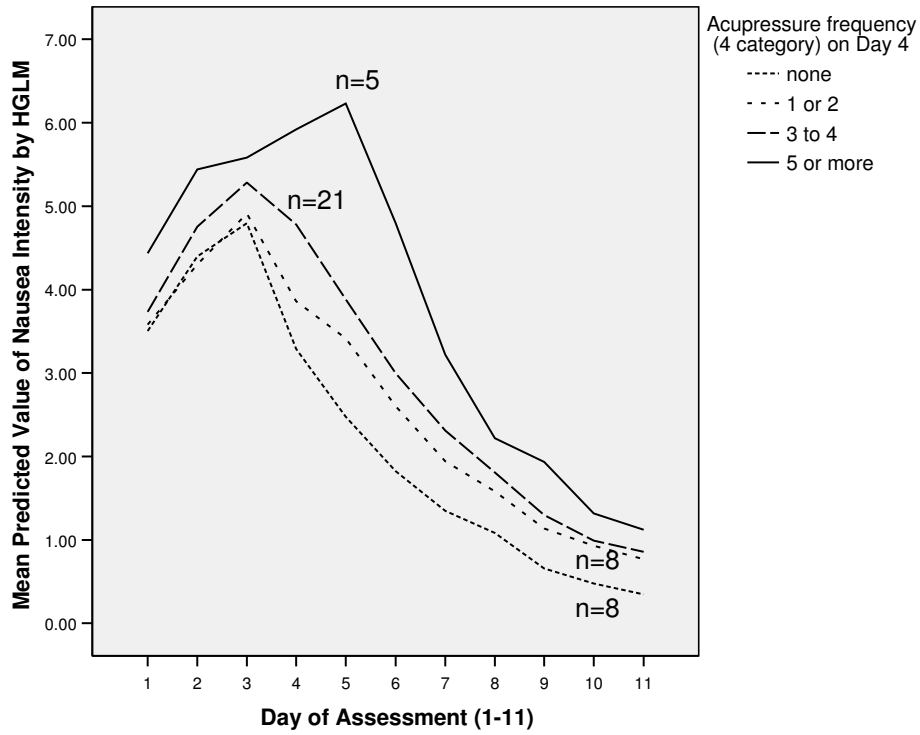


Figure 4. Predicted Value of Nausea Intensity:
Four Category Acupressure Frequency on Day 4 Variable into HGLM

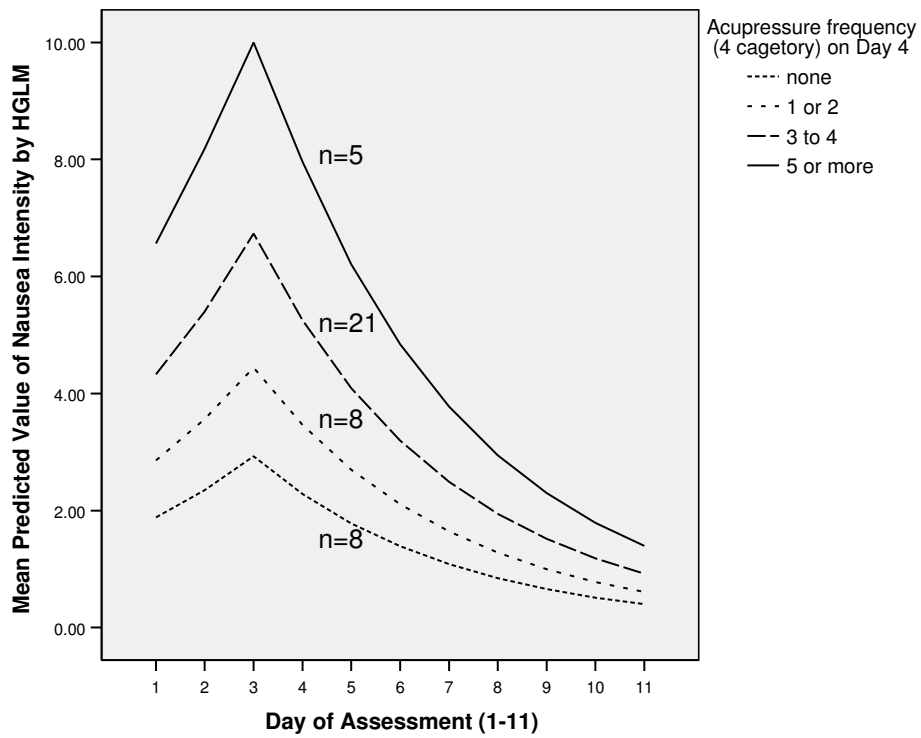
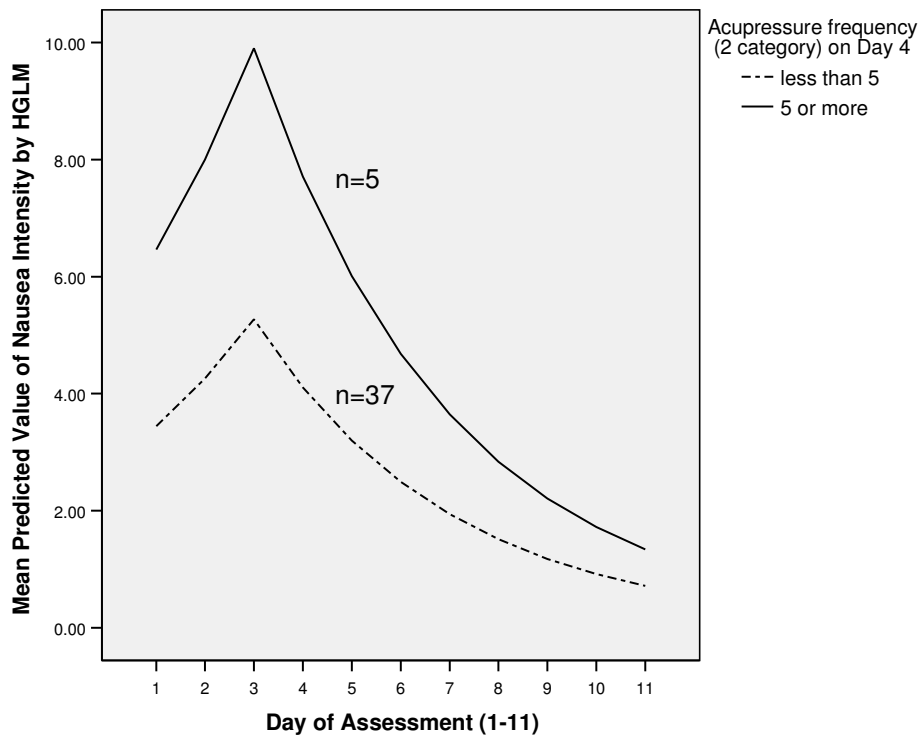


Figure 5. Predicted Value of Nausea Intensity:
Two Category Acupressure Frequency on Day 4 Variable into HGLM



Chapter 3.

Nausea at the End of Adjuvant Cancer Treatment is Related to Exercise
during the Treatment in Breast Cancer Patients

Podium presentation at the 32nd Oncology Nursing Society Congress,
Las Vegas, Nevada, April, 2007

Lee, J., Dodd, M, Dibble, S., & Abrams, D

Oncology Nursing Forum, in press

Abstract

Purpose/Objectives: To evaluate the relationship between nausea and exercise during and after adjuvant cancer treatment (chemotherapy +/- radiation therapy).

Design/Research Approach: Secondary data analysis from a longitudinal, single blinded, three-arm, randomized controlled trial. The trial failed to show a significant effect of an exercise intervention for nausea control (by intent to treat analysis), therefore patients were analyzed together to evaluate the relationship between nausea and actual exercise behavior.

Setting: Outpatient cancer treatment clinics.

Sample/Participants: One hundred and twelve female breast cancer patients who were receiving adjuvant cancer treatment.

Methods: Actual exercise behavior-based analysis was conducted with the nausea intensity and the participant's exercise status measured three times during and after adjuvant cancer treatment. Participants were considered as exercisers if actual exercise behaviors were corresponding to the recommendation of the American College of Sports Medicine (1998): the undertaking of aerobic exercise at a minimum of moderate intensity, 20 minutes per session, and three times per week. The Mann-Whitney U test evaluated the difference in nausea intensity depending on actual exercise status.

Main Research Variables: Nausea intensity, exercise status.

Findings: Exercisers experienced significantly less intense nausea than non-exercisers at the completion of adjuvant cancer treatment ($p = .03$).

Conclusions: A moderate level of aerobic exercise is related to less intense nausea at the completion of adjuvant cancer treatment.

Implications for Nursing: A moderate level of aerobic exercise is recommended during adjuvant cancer treatment considering the possibility of declining nausea intensity as well as the benefits of alleviating other symptoms from adjuvant cancer treatment.

Key Words: nausea, exercise, adjuvant cancer treatment, breast cancer

Introduction

Nausea remains one of the most distressful side effects of chemotherapy (de Boer-Dennert et al., 1997; Lindley et al., 1999). Control of chemotherapy-induced vomiting has improved with the development of antiemetic guidelines and new antiemetics such as aprepitant and palonosetron (Kris et al., 2006; National Comprehensive Cancer Network, 2007; Roila, Hesketh, & Herrstedt, 2006). However, current nausea control with antiemetics continues to be inadequate. Forty-seven percent of patients suffered delayed nausea and 29% of patients reported acute nausea even with the combined use of the newest antiemetics such as palonosetron and aprepitant with moderately emetogenic chemotherapy in a sample of 58 patients with diverse cancers (Grote et al., 2006). The incidence of delayed nausea with the use of standard antiemetics was much higher among 569 cancer patients with diverse cancers treated with highly emetogenic chemotherapy as 52% experienced the symptom (Hesketh et al., 2003). The overall incidence of nausea among 866 breast cancer patients receiving moderately emetogenic chemotherapy with standard antiemetics was 67% (Herrstedt et al., 2005). Clearly, additional intervention is needed.

Exercise has been suggested as a possible intervention for cancer-related symptoms (American Cancer Society, 2007). In considering exercise as an intervention for cancer patients, exercise guidelines provide specifics for the exercise regime, such as the mode, intensity, duration, and frequency. In 1998, the American College of Sports Medicine (ACSM) recommended to undertake aerobic exercise of moderate intensity for 20-60 minutes per session, 3-5 times per week (ACSM, 1998). Exercise has shown positive effects in controlling well-known and prevalent symptoms in cancer patients,

such as fatigue (Mitchell, Beck, Hood, Moore, & Tanner, 2007; Mock et al., 2005; Mock et al., 2001; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a, 2007b). However, studies of exercise for nausea control are limited and provide inconsistent results.

Winningham and MacVicar (1988) first reported researching the positive effects of exercise on nausea control. Repeated verbal reports from participants about the effects of exercise in controlling their nausea during a pilot trial stimulated the researchers to investigate further. Their randomized clinical trial (RCT) included 42 female breast cancer patients receiving chemotherapy. Participants were randomized to an exercise group, a placebo group, or a control group. Aerobic exercise on a cycle ergometer prescribed to reach 60-85% of maximal heart rate was performed by patients in the exercise group, three times a week for 10 weeks. The placebo group performed stretching and flexibility exercise but not an aerobic exercise. The control group did not perform any exercise. The 16 participants in the exercise group demonstrated marked improvement with less nausea compared to the placebo and control groups ($p = .03$). No antiemetics were administered, though all participants were on moderately emetogenic chemotherapy regimens including cyclophosphamide, methotrexate, and 5-fluorouracil. Suboptimal control of nausea during this evaluation of exercise effect could raise the question of whether the achieved exercise effect on nausea control could be reproduced when antiemetics were used according to current antiemetic guidelines.

Mock et al. (1994) conducted a RCT with 14 female breast cancer patients. The exercise intervention was a brisk incremental walking of 10-45 minutes followed by five minutes cooling down period, 4-5 times a week for 4-6 months. The exercise intervention was a part of comprehensive rehabilitation program that consisted of a structured exercise

program which included walking plus support group meetings for 4-6 cycles of chemotherapy. A significant difference in the intensity level of the nausea was found at the mid-treatment testing (day 15 of every chemotherapy cycle) ($p = .02$). No statistically significant difference was found between the exercise group and usual care group when the mean nausea intensity level was compared across all the periods of treatment, although the usual care group did report more nausea. It is questionable if the exercise has any time-specific effects in controlling the nausea. It is difficult to separate the exercise effect from the comprehensive rehabilitation program because the intervention was combined with support group meetings. The small sample size of only nine exercisers is also an issue. Additionally, antiemetic use was not controlled, although participants received moderate to highly emetogenic chemotherapy.

Unlike the two previous studies on exercise, the study by Schwartz (2000) did not find an exercise effect on nausea. Eight weeks of home-based progressive aerobic exercise was performed during the first four cycles of chemotherapy. Participants were all breast cancer patients receiving moderate to highly emetogenic chemotherapy (doxorubicin and cyclophosphamide, or cyclophosphamide, methotrexate, and 5-fluorouracil) and were instructed to perform exercise four days a week, with a progressive increase in the duration and intensity of their exercise. Antiemetic use was not controlled. The women who adhered to the program reported walking as the most common activity and exercised an average of 33 minutes per exercise session. Whether the intensity of the exercise was high enough to produce an exercise effect in controlling nausea was not reported in the study.

The most recent exercise study by Andersen et al. (2006) combined six weeks of physical activity with relaxation, massage, and body awareness training. The researchers reported that nausea intensity levels did not change after the intervention among the cancer patients, who had diverse cancer diagnoses ($N = 54$). The physical activity of this intervention consisted of 90 minutes of warm up, heavy resistance training, and fitness activities. The fitness component consisted of 10 minute interval exertions in the form of cycling on stationary bicycles with an intensity of 80-100% of the participant's maximum heart rate, three times per week. It is of interest that the nausea scores were slightly increased after the exercise intervention although the change did not reach statistical significance. It is questionable if the 10 minutes of cycling as aerobic exercise was long enough to influence the level of nausea or if the high intensity of the aerobic exercise or heavy resistance training had any adverse effect in nausea control. It is also difficult to evaluate the exercise effect separately because the intervention was a packaged intervention. All patients in this trial received antiemetic drugs including 5-HT₃ RA, metoclopramide, and/or prednisone. The exercise could have not been enough to provide additional CINV control with these antiemetics.

To summarize, four studies were found that investigated the effects of exercise on the control of nausea. Two studies supporting the effects of exercise on nausea had issues with small sample sizes and uncontrolled use of antiemetics. Studies that combined exercise with other interventions made the evaluation of exercise effects alone difficult. The results of the Schwartz (2000) and Andersen et al. (2006) studies contradict reported positive effects of exercise on nausea control. However, it is likely that in the Schwartz study, the intensity of exercise performed by the participants did not reach the established

“moderate” exercise level to make a difference in the incidence of nausea. The Anderson et al. study had issues including its short duration of a higher than moderate level of exercise, in combination with heavy resistance training. Further research is required before recommending a moderate level of aerobic exercise to control nausea.

The purpose of this study is to evaluate the relationship between nausea intensity and a moderate level of aerobic exercise recommended by the ACSM (1998) during and after adjuvant cancer treatment (chemotherapy +/- radiation therapy). The theoretical framework for this study is the UCSF Symptom Management Model (Dodd et al., 2001). This study is focused on nausea as a symptom experience, exercise for its management, and nausea intensity as an outcome.

Methods

Design

This study is a secondary analysis of data collected as part of a longitudinal, randomized controlled trial that tested the effectiveness of a systematic exercise intervention for cancer related fatigue and associated symptoms. In the trial, participants were randomized into three groups who were comprised of a group receiving exercise prescription throughout the study period, a group starting to receive exercise prescription after having completed their cancer treatment, and a group receiving usual care throughout the study period. Researchers were blinded as to the participant’s group assignment when collecting data. The trial failed to show significant effect of an exercise intervention for nausea intensity control (by intent to treat analysis). Therefore, patients were analyzed together to evaluate the relationship between nausea and actual exercise behavior.

Sample and Setting

Participants were recruited from six outpatient cancer treatment clinics in the counties of the San Francisco Bay Area. Inclusion criteria included women who 1) were 18 years or older; 2) had a confirmed diagnoses of breast cancer; 3) were beginning their first cycle of chemotherapy; 4) were able to read, write, and understand English; 5) had a Karnofsky Performance Scale (KPS) score of > 60, and 6) were mentally able to understand and complete a written informed consent. Participants were excluded from the study if they 1) had uncontrolled hypertension or diabetes mellitus, 2) had a pain intensity rating of 3 or higher on a 0-10 numeric scale, 3) had a lytic bone lesion or orthopedic limitations, 4) were receiving concurrent radiation therapy or bone marrow transplant, 5) had a history of major depression or sleep disorders, 6) had chemotherapy within the past year, 7) had a diagnosis of AIDS-related malignancies or leukemia, or 8) absolute contraindications to exercise testing as established by the ACSM (ACSM, 1995).

Instruments

Nausea intensity, exercise status, and KPS score were measured through participant self-report. Nausea intensity was measured using a 0-10 numeric scale (patients were asked how much they were experiencing nausea at the time of data collection). The nausea intensity scale was derived from the symptom checklist of 25 commonly experienced symptoms. The symptom checklist has been used in studies of one of the authors (Dodd) to collect data about concurrent symptoms. The 0-10 numeric scale has been tested in parallel with the use of a well-known nausea instrument, the Index of Nausea Vomiting and Retching (INVR, Rhodes & McDaniel, 1999), in studies of chemotherapy-induced nausea and vomiting and has yielded high correlations ($r = .75-$

.95) with the INVR nausea experience score (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Lee, Dibble, Pickett, & Luce, 2005). Exercise status was measured as the type of exercise (mode), intensity of exercise (intensity), time per session (duration), and number of days per week (frequency). Functional status was measured by KPS scores (0-100).

Procedures

Actual exercise behavior-based analysis was conducted with the nausea intensity and the participant's exercise status measured three times during and after adjuvant cancer treatment. The three data collecting time points were between completion of the first cycle and the start of the second cycle of chemotherapy (T1), at the end of adjuvant cancer treatment (T2) and at the end of the study (T3, approximately one year later after the start of chemotherapy) (Figure 1). Participants were regarded as performing exercise (exerciser) if actual exercise behaviors measured at each time points by the mode, intensity, duration, and frequency of exercise corresponded to the recommendation of the ACSM (1998): as engaging in aerobic exercise at a minimum of moderate intensity for 20 minutes per session three times per week. The intensity of the exercise was regarded as more than moderate if the exercise rating on the Borg Scale was equal to or higher than 12 (Borg, 1998). The Borg Scale measures perceived exertion upon physical activity. It is considered as a physical activity of moderate intensity when the Borg Scale rating is between 12 and 14 which are interpreted as "somewhat hard" (Box 1).

Data Analysis

Data were analyzed with descriptive statistics, Mann-Whitney U test, T-test, and Chi-square test at alpha of .05 using the SPSS 14.0 for Windows™. The Mann-Whitney

U test was used because the scores for nausea intensity were relatively low and skewed in their distribution. The Mann-Whitney U test is a nonparametric test which does not assume normal distribution of the variable in the population and analogous to the T-test as it is used to compare two groups. Scores of subjects are converted into ranks, and the analyses compare the mean ranks in each group (Munro, 2005).

Results

A total of 112 female breast cancer patients participated in the study. The mean age of participants was 50 years ($SD = 9.31$) and most were Caucasian (73.2%). Participants' education level was high (mean years of education = 16, $SD = 2.76$). Forty-four percent of participants worked either full-time (33%) or part-time (10.7%). Most were married or partnered (67.9%). The stage of breast cancer ranged from stage I-III. Ninety-eight participants (87.5%) received doxorubicin and cyclophosphamide as a chemotherapy regimen, and 59 (52.7%) received radiation therapy immediately after finishing chemotherapy. Antiemetics were used with chemotherapy; however, only 30 participants provided information about their use of antiemetics. Ondansetron, granisetron, dexamethasone, metochlopramide, and lorazepam were used but not in a standardized fashion. No participant received antiemetics at the time of the three assessments. The number of exercisers according to the ACSM recommendation at T1 was 52. The number decreased to 45 at T2, and increased to 67 at T3. The average length of time between T1 and T2 was 169.72 days ($SD = 65.09$) and the time between T2 to T3 was 165.64 days ($SD = 61.72$). There were participants who dropped out over study period. An analysis about demographic data of participants who dropped and those who did not showed non-significant differences between these two groups other than receiving

radiation therapy after chemotherapy. Significantly more participants who dropped at T2 ($p = .01$) or T3 ($p = .05$) did not receive radiation therapy after chemotherapy. However, exercisers and non-exercisers at T2 or T3 were not different whether they received radiation therapy after chemotherapy or not. Among exercisers, up to 88% of the women chose walking as their exercise and 33% chose bicycling either by cycle ergometer or bicycle (Table 1).

Sixty-six percent of women experienced nausea during the study period. Nausea intensity was generally low and decreased over time (Table 2). The average nausea intensity score was 1.6 at T1, 0.96 at T2, and 0.35 at T3 in the 0-10 nausea intensity scale. The intensity of nausea was compared between exercisers and non-exercisers to evaluate relationship of exercise and nausea intensity. Mean nausea intensity was lower in exercisers at T1 and T2, whereas non-exercisers had a little less nausea at T3 (Table 3). Nausea intensity for exercisers at T2 was statistically lower than that for non-exercisers by the Mann-Whitney U test ($p = .03$) as shown in Table 4. Baseline (T1) and T3 nausea intensity scores did not differ significantly between exercisers and non-exercisers. The intensity of nausea in exercisers had declined at T2 so as to produce significantly lower nausea intensity scores compared to the non-exercisers. Exercisers had almost no nausea at T2, whereas non-exercisers had significantly higher nausea intensity and decreased levels similar to those of exercisers at T3 (Figure 2). Exercisers and non-exercisers did not differ in age, stage of breast cancer, KPS, whether they received doxorubicin and cyclophosphamide as a chemotherapy regimen, or received radiation therapy immediately after their chemotherapy.

There were two groups of exercisers at T2. Some participants in our study were regular exercisers at the time of recruitment and continued to exercise during adjuvant cancer treatment ($n = 27$). There were other participants who were not exercisers as they enrolled in study but became exercisers during cancer treatment ($n = 12$). At T2, the regular exercisers who continued their exercise during adjuvant cancer treatment experienced less intense nausea (mean nausea intensity score = .37) than did the participants who became exercisers during cancer treatment (mean nausea intensity score = .83). However, there was no statistically significant difference between two groups in nausea intensity ($p = .10$). This suggests no accumulative effect of exercise in its relationship to nausea intensity.

Discussion

Reported levels of nausea intensity in this study were generally low. Although a significant difference was found at T2, the level of nausea intensity in non-exercisers did not reach the level generally considered to be “significant nausea” (≥ 25 mm on a 0-100 VAS scale). However, it is remarkable that the nausea at T2 of exercisers were at the level generally considered “no nausea” (< 5 mm on a 0-100 VAS scale) (Herrstedt et al., 2005; Hesketh et al., 2003; Poli-Bigelli et al., 2003; Schmoll et al., 2006; Warr, Grunberg et al., 2005; Warr, Hesketh et al., 2005).

The exercise intervention of Winningham and MacVicar (1988), which involved aerobic exercise on a cycle ergometer of moderate intensity, three times a week, for 10 weeks was similar to the exercise performed by the defined exerciser in our study, and both studies found a significant relationship between nausea and exercise. However, the Winningham and MacVicar study did not use antiemetics, even with moderately

emetogenic chemotherapies. The participants in this study did not take any antiemetics at each time point (T1, T2, and T3), however, non-standardized antiemetic regimens were used during chemotherapy based on reports from 30 participants. Non-use or non-standardized use of antiemetics during the chemotherapy intervention raises the question whether the suggested exercise effect could be reproduced after use of standard antiemetics.

In the study of Mock et al. (1994), the participants could be categorized as an exerciser if their duration of exercise was more than 20 minutes. Mock et al. found an exercise effect at the middle of treatment (15 days of each chemotherapy cycle) but not in overall nausea scores. The nausea difference found in this study occurred after the completion of adjuvant cancer treatment (T2) but not at other time points. Although both studies suggest time-specific effects of exercise in nausea control, the time points of our study do not correspond with the points of Mock et al. Further research is required to reach better conclusions about any time-specific effects of exercise on nausea control because this study did not evaluate nausea while patients were receiving adjuvant cancer treatment.

The two other exercise studies (Andersen et al., 2006; Schwartz, 2000) that also investigated aerobic exercise as an intervention for nausea control were different in the content of their exercise programs (i.e., suboptimal intensity or duration) and did not demonstrate a significant exercise effect on nausea control. Whether different results were derived within a different exercise context needs further investigation.

Participants in other exercise studies performed exercise while undergoing chemotherapy, whereas participants in our study also exercised after the treatment (i.e.,

during the follow-up). This enables further evaluation about the need of exercise during additional periods of time. Our study and other exercise studies that describe positive effects on nausea control support exercising during adjuvant cancer treatment.

The mechanisms by which exercise improves the control of nausea have not been established. Proposed mechanisms of nausea development such as involvement of the central nervous system (Leslie, 1993; Miller, Rowley, Roberts, & Kucharczyk, 1996), by an increase in vasopressin secretion and activation in autonomic nervous system (Stern, 2002) need further investigation. Evidence that exercise may decrease levels of vasopressin (Braith, Welsch, Feigenbaum, Kluess, & Pepine, 1999) and also decrease sympathoexcitation (Gademan et al., 2007) at rest among chronic heart failure patients suggests a possible link between nausea and exercise through vasopressin and the autonomic nervous system regulation in the central nervous system.

It is of interest that the study by Andersen et al. (2006) found a slight increase in nausea scores after the exercise intervention, although the increase was not statistically significant. High intensity of exercise (70-80% of maximal heart rate) is related to higher ratings of nausea (Kondo et al., 2001). The exercise intervention in the study by Andersen et al. (2006) might have caused more nausea as 10 minutes on stationary bicycles with an intensity of 80-100% of maximal heart rate is quite intense exercise. However, the intervention in the Andersen et al. study included several exercise interventions besides 10 minutes of cycling, which increased the difficulty in interpreting the exercise effect.

The number of exercisers increased from T2 to T3. As the parent study was designed to increase the number of participants receiving the exercise prescription

between T2 and T3, this increase may be due to the study design. However, this may also be due to the women who had recovered after their adjuvant cancer treatment completion being more inclined to exercise regardless of the exercise intervention in the parent study.

The most preferred exercise in this study was walking, which was also true in the studies by Schwartz (2000) and Rogers et al. (2007). Walking can be easily accepted as an exercise intervention for breast cancer patients during adjuvant cancer treatment; however, the context of exercise (i.e., mode, intensity, duration, and frequency) is more of a concern. The use of the 1998 ACSM guideline for exercise in cancer patients was associated with less intense nausea at T2 of this study, and the exercise effect in nausea control was found in the study by Winningham and MacVicar (1988) and partly in the study by Mock (1994). Exercise intervention at a minimum criteria set by the ACSM recommendation (1998) is suggested for future exercise studies during adjuvant chemotherapy.

Limitations and Future Directions

There are several limitations of our study to consider. First, nausea intensity was not measured during adjuvant therapy, especially during chemotherapy, which is a period of intense nausea. Furthermore, exercise status was determined only at three points (T1, T2, and T3). More frequent data (i.e., daily) would have provided detailed information about the exercise effects on nausea intensity. Second, nausea was measured unidimensionally, and other aspects of nausea such as duration and distress were not evaluated. Although there are studies that support the use of the numeric rating scale as a measure of nausea based on significant correlation with other multi-dimensional nausea measure from the INVR (Rhodes & McDaniel, 1999), further research is required

because some discrepancies have been found between the numeric rating scale and other measures for nausea on a daily basis (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Lee, Dibble, Pickett, & Luce, 2005). Another issue in nausea measurement of this study was at T1 measurement. The nausea rating scale used in this study was not phrased as to discriminate nausea from the anticipation of next chemotherapy or nausea that continued after last chemotherapy. It is difficult to determine if the nausea at T1 was anticipatory or delayed nausea.

Finally, as the actual behavior-based analysis was performed, the benefit of randomization was not conserved. A causal relationship between exercise and nausea could not be supported even with the significant difference of nausea intensity according to exercise status, and no difference was found in age, stage of breast cancer, KPS score, chemotherapy regimen or in those receiving radiation therapy after their chemotherapy. Although it is highly suggestive that those who exercised had less intense nausea at T2, it is also possible that those who had less nausea were more motivated to perform an exercise program.

Conclusion

Breast cancer patients who performed a moderate level of aerobic exercise during adjuvant cancer treatment experienced less intense nausea at the treatment completion. A moderate level of aerobic exercise is recommended during adjuvant cancer treatment considering its possibility of supporting a decline in nausea intensity as well as the benefits of alleviating other symptoms from adjuvant cancer treatment. Further study is recommended to evaluate the effect of a moderate level of aerobic exercise, as

recommended by the ACSM (1998), in addition to antiemetics in controlling nausea during the period of intense nausea such as few days after chemotherapy.

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Box 1. Definition of Exerciser

Participants who conducted aerobic exercise at a minimum of

- Frequency: 3 times/week
- Duration: 20 minutes/session
- Intensity: moderate (≥ 12 in Borg Scale)

Table 1. Number of Exercisers and Non-Exercisers ($N = 112$)

	Exerciser	Non-Exerciser	Missing
T1	52	52	8
T2	45	52	15
T3	67	26	19

Table 2. Nausea Intensity of Participants at Each Time Point ($N = 112$)

	<i>Mean</i>	<i>SD</i>
T1	1.60	2.26
T2	0.96	1.94
T3	0.35	0.83

Table 3. Nausea Intensity of Exercisers and Non-Exercisers

	Exerciser		Non-Exerciser	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
T1	1.55	2.49	1.69	2.08
T2	0.47	1.31	1.40	2.31
T3	0.38	0.91	0.32	0.69

Table 4. Mann-Whitney U Comparison of Nausea Intensity of Exercisers versus Non-exercisers

	Z score	<i>p</i> -value
T1	-1.06	.29
T2	-2.18	.03*
T3	-0.09	.93

* $p < .05$

Figure 1. Design of the Study

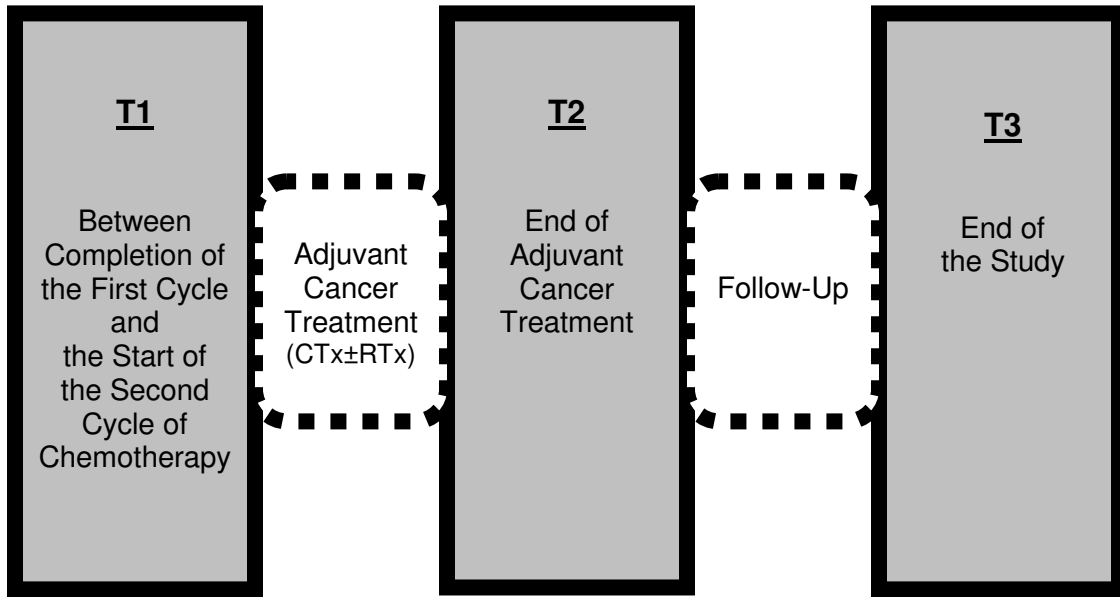
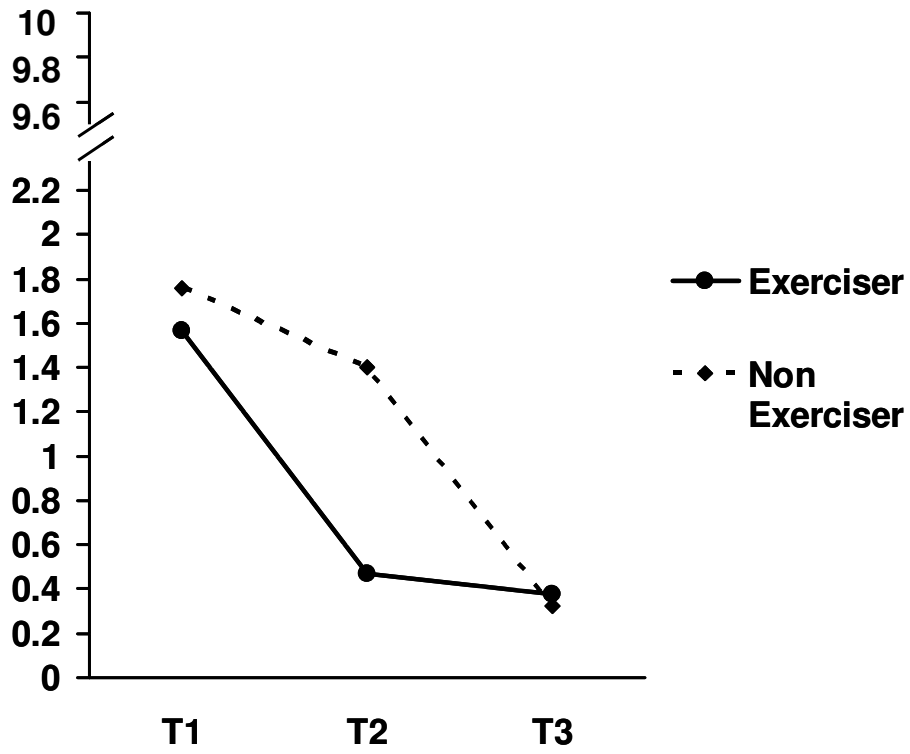


Figure 2. Change in Nausea Intensity



Chapter 4.

Chemotherapy-Induced Nausea/Vomiting and Functional Status in Women Treated for Breast Cancer

Lee, J., Dibble, S., Pickett, M, & Luce, J

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Abstract

Nausea and vomiting are among the most distressing symptoms for cancer patients treated with chemotherapy even with the widespread use of 5-HT₃ antagonists. Chemotherapy-induced nausea and vomiting (CINV) is composed of four major components: acute nausea, delayed nausea, acute vomiting and delayed vomiting. Determining the relationship of each component of CINV on the functional status of women undergoing chemotherapy for breast cancer was the purpose of this study. This longitudinal, descriptive study over two months of chemotherapy recruited 303 breast cancer patients from 40 study sites in the United States. Reliable and valid measures of CINV and functional status were employed. Patients demonstrated significant decreases in the following aspects of functional status as measured by the SF-36: physical functioning ($p < .001$), role limitations due to physical problems ($p = .003$), general health ($p = .029$), vitality ($p < .001$), and social functioning ($p = .001$). The pattern of reduction in usual activities and increase in hours of resting correlated best with two components of CINV: delayed nausea and vomiting ($p < .001$, each). The results of this study suggest that control of delayed CINV may contribute to the functional improvement of women receiving chemotherapy for breast cancer.

Key Words: chemotherapy, nausea, vomiting, functional status, breast cancer

Introduction

Nausea and vomiting are among the most distressing side effects of chemotherapy (Rhodes & McDaniel, 2001). Despite steady improvements in antiemetic drug treatments over the last two decades, about 55% of cancer patients suffer from these symptoms during the first 5 to 7 days of chemotherapy (Gralla et al., 1999). Prior research suggests that the functional status of patients can be compromised by chemotherapy (Broeckel, Jacobsen, Balducci, Horton, & Lyman, 2000; Chie, Huang, Chen, & Chang, 1999; Grunfeld et al., 1996; Hurny et al., 1996; Lindley, Vasa, Sawyer, & Winer, 1998; Lindley, Bernard, & Fields, 1989; Maguire et al., 1980; Pandey et al., 2000) and the adverse effects of nausea and vomiting (Farley et al., 1997; O'Brien et al., 1993; Osoba et al., 1997; Palmer, Walsh, McKinna, & Greening, 1980; Rusthoven et al., 1998). Almost half of breast cancer patients who had received chemotherapy indicated that it had caused severe disruption in their lives (Lindley, Vasa, Sawyer, & Winer, 1998). The chemotherapy phase of breast cancer treatment has been associated with the poorest functional status when compared with other phases of treatment (Chie, Huang, Chen, & Chang, 1999).

Patients who reported experiencing both nausea and vomiting during chemotherapy treatment have reported lower functioning in physical, cognitive, and social dimensions when compared with patients who did not report nausea and vomiting during their chemotherapy treatment (Osoba et al., 1997). Most functional changes in one quality of life study could be attributable to chemotherapy-induced nausea and vomiting (CINV) (Rusthoven et al., 1998). Farley and colleagues also suggested that patients' perceived functional status was related to freedom from CINV (Farley et al., 1997).

However, studies about chemotherapy and change in functional status included diverse cancer patient groups (Farley et al., 1997; O'Brien et al., 1993; Osoba et al., 1997; Rusthoven et al., 1998), although many of them were comprised of breast cancer patients. Functional status was measured more than two months after the chemotherapy (Broeckel, Jacobsen, Balducci, Horton, & Lyman, 2000; Grunfeld et al., 1996; Hurny et al., 1996; Lindley, Vasa, Sawyer, & Winer, 1998; Maguire et al., 1980; Mosconi et al., 2002; Palmer, Walsh, McKinna, & Greening, 1980; Pandey et al., 2000), to examine the residual, long term impact of chemotherapy rather than the short term influence of CINV. The short span influence of CINV on functional changes needs to be discriminated. CINV is distinguished as 'acute' which occurs within 24 hours of the administration of chemotherapy (Hesketh, Gralla, du Bois, & Tonato, 1998; Lindley, Bernard, & Fields, 1989) and 'delayed' that occurs after the first 24 hours (Dicato, 1996). The number of days included in the concepts of delayed nausea or delayed vomiting has varied with a particular study; thus there is no consensus as to the actual time composition of delayed nausea or delayed vomiting. Nausea occurs more frequently than vomiting after chemotherapy (Gralla et al., 1999). Also, studies conducted before 5-HT₃ antagonists became available (Maguire et al., 1980; O'Brien et al., 1993; Palmer, Walsh, McKinna, & Greening, 1980) do not contribute to understand the impact of CINV on the functional status of breast cancer patients receiving standard antiemetics that currently include 5-HT₃ antagonists.

The purpose of this study was to assess the functional status of breast cancer patients during two cycles of chemotherapy in the era of widespread use of anthracyclines and 5-HT₃ antagonists, and to evaluate the influence of acute and delayed

CINV.

Methods

Sample and Setting

Patients who were female, receiving any emetogenic chemotherapy regimen for adjuvant treatment of a confirmed diagnosis of breast cancer, able to communicate in English (both oral and written), and had at least two months left in their treatment plan were eligible to participate in the study. Out of 353 patients who were initially approached to participate, 303 completed the study. Fifty patients (14%) chose not to participate and “feeling overwhelmed” was the most common reason for refusal.

The study sample was recruited at 40 outpatient oncology clinics; both urban and rural sites participated including: 7 clinics located in community hospitals, 5 clinics associated with major universities, 27 private oncology practices, and 1 clinic located in a public hospital. The sites were located in the West, North East, and Midwestern United States and one site in Virginia.

Design

This study was designed as a longitudinal, descriptive study over two months of chemotherapy treatment to describe the nausea and vomiting experiences as well as changes in breast cancer patients’ functional status over time. The study was also aimed to explore the relationship between CINV and functional status.

Instruments

Patient Information Questionnaire (PIQ). The Patient Information Questionnaire (PIQ) is an instrument designed to collect demographic data, including age, education, partnership status, race/ethnicity, employment status, and income. PIQ also includes

questions about history of carsickness, seasickness, nausea with stress, and morning sickness.

Disease and Treatment Questionnaire (DTQ). The Disease and Treatment Questionnaire (DTQ) includes items such as diagnosis date, surgical treatment, type of breast cancer, treatment regimens, chemotherapy dosages, reduction in dosages, anti-emetics taken via intravenous administration or orally as well as any changes in their anti-emetic protocol.

Daily Log. The daily log included three nausea and three vomiting items selected from the Rhodes Index of Nausea, Vomiting, and Retching (INVR) (Rhodes & McDaniel, 1999; Rhodes, Watson, Johnson, Madsen & Beck, 1987). Items measure the amount of time woman experienced nausea, the amount of vomiting, the distress that the nausea (and/or vomiting) produced, and the number of times that nausea (and/or vomiting) occurred in 24 hours. Acute nausea and vomiting were measured on treatment day (Day 0), and delayed nausea and vomiting were evaluated during the first 10 days after the treatment (Day 1 to 10). A daily scale ranged from 0 to 12, with higher scores reflecting a more severe symptom experience. Scores for each of 10 days were summed to create a delayed nausea scale (ranged from 0 to 120) and a delayed vomiting scale (same range of scores). The INVR has established reliability and validity (Cronbach's $\alpha = .98$, concurrent validity $r = .87$) (Rhodes & McDaniel, 1999; Rhodes, Watson, Johnson, Madsen, & Beck, 1987). After piloting the instrument with similar women being treated for breast cancer, the retching items were eliminated because of time and concerns expressed about the items from the women. In this sample, the Cronbach's α for the nausea subscale was .93 and for the vomiting subscale, .92.

Additionally, the daily log also included two numeric rating scale (NRS) items to evaluate daily nausea and vomiting. Participants rated their day's nausea and vomiting on these 0 to 10 scales. We used these items to see if we could eventually decrease the amount of work required of the participants in our nausea trials by replacing the 6 items of the INVR with these two items. Indeed the correlation between the nausea subscale of the INVR and the nausea NRS was .92 and the correlation between the vomiting subscale of the INVR and the vomiting NRS was again .92.

Daily functional status was measured using two items. The first item was usual activities that patients were able to perform in the last 24 hours and it was rated on a 0 to 10 NRS. The second item was the number of hours that a patient spent resting in bed or on a couch/sofa (not sleeping at night). Participants were instructed to perform the ratings on a daily basis, prior to bedtime. Patients also recorded the pharmaceutical and non pharmaceutical interventions that they used to control their nausea and vomiting on a daily basis.

Medical Outcomes Study Short Form (SF-36). The SF-36 consists of 36 items that include a multi-item scales that measures eight concepts: physical functioning, role limitation due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitation due to emotional problems (role-emotional), and mental health. All of these concepts are appropriate to use in exploring an individual's functional status. The SF-36 has established validity and reliability in a broad range of populations (McHorney, Ware, Lu, & Sherbourne, 1994).

Procedures

The study was conducted after receiving approval from each Institutional Review Board of participating institutions in the study. Potential study participants were approached about the study by trained research assistants, physicians, or nurses. After completing the consent form, participants' baseline data, including demographic data and Medical Outcomes Study Short Form (SF-36), were collected and participants were taught how to complete the daily log. Participants recorded in their log daily for approximately two months (two cycles of standard therapy). Women who were receiving chemotherapy on a weekly basis were asked to complete the daily log for three weeks per log. At the end of the study, approximately a month after finishing a second cycle of chemotherapy, participants completed a second SF-36 to evaluate their functional status. Patients' medical records were abstracted by nurses who had received training about the conduct of the study either in person or via the telephone.

Statistical Analysis

The SPSS® statistical software package version 11 (SPSS, Inc., Chicago, IL) was used for data analysis. Descriptive statistics were generated related to sample characteristics and occurrence of CINV. Repeated measures analysis of variance (ANOVA) was used to determine the change over time in usual activities and hours of resting. The changes in SF-36 subscales before and after treatment were analyzed using paired t-test. Relationships among chemotherapy induced nausea, vomiting, usual activities and hours of resting were tested using Pearson correlations. Two methods of imputation strategies (mean substitution and last value carried forward) were utilized to handle some of the problems of missing values (Statistical Solutions, 1997). The most

common reason for missing values was when participants stopped recording in their log after a number of days of no nausea or vomiting or they skipped a day of recording. Level of significance of $\alpha = .05$ (two-tailed) was applied to all statistical analyses.

Results

Patient Characteristics

The mean age of 303 women included in this study was 51.9 years (range, 28-86). The typical woman in this study was Caucasian (79%), married/partnered (65%), not disabled (86%), unemployed (52%), not living alone (84%), more than high school educated (56%), and having an annual personal income of more than \$20,000 (58%). Most women did not experience nausea while at sea (24%), riding in a car (20%), or with stress (22%); however most women (60%) did experience nausea while pregnant (Table 1).

The average time since diagnosis was approximately two months. Cancer diagnosis represented in the sample included 238 patients (80%) with infiltrating ductal cancer, and 25 patients (8%) with infiltrating lobular cancer. Surgical intervention for 113 patients (37%) was mastectomy, and 190 patients (63%) had lumpectomy. Eighty percent of the patients received lymph node dissection.

Most patients were receiving adjuvant chemotherapy on a cyclical basis (93%) and received cyclophosphamide + doxorubicin as their chemotherapy regimen (76%), followed by cyclophosphamide + methotrexate + fluorouracil (11%). The average dose of cyclophosphamide among 268 patients was 543.2 mg/m^2 ($SD = 134.4 \text{ mg/m}^2$), doxorubicin among 254 patients was 56.0 mg/m^2 ($SD = 7.7 \text{ mg/m}^2$), and fluorouracil among 40 patients was 514.1 mg/m^2 ($SD = 126.5 \text{ mg/m}^2$). Only 14 patients (5%) of the

sample had chemotherapy dose reductions during their second cycle. Radiation therapy had been completed or was concurrent with chemotherapy in 7% ($n = 19$) of the sample and 61% ($n = 171$) were planning radiation therapy after completing chemotherapy (Table 2).

The most common intravenous antiemetics received by study participants were dexamethasone (80%), ondansetron (49%), granisetron (24%), and dolasetron (17%). Only 6% ($n = 18$) had their intravenous antiemetics changed between the two cycles of chemotherapy. Prochlorperazine (70%) was the most common oral antiemetic ordered for home use, followed by ondansetron (38%), and dexamethasone (23%). The type of oral antiemetics was changed between the two cycles of the study in 8% ($n = 24$) of patients.

Functional Status

Patients' functional status before and after two cycles of chemotherapy was measured by SF-36 and each score of the subscale was converted into a scale of 0 to 100. Higher scores mean better function. Physical functioning ($p < .001$), role-physical ($p = .003$), general health ($p = .029$), vitality ($p < .001$), and social functioning ($p = .001$) deteriorated significantly after two cycles of chemotherapy. There was no difference in the role-emotional subscale ($p = .893$). Bodily pain ($p < .001$) and mental health status ($p < .001$) were significantly improved after two cycles of chemotherapy (Table 3).

The daily impact of chemotherapy on functional status was obtained through analysis of patients' reports of usual activities as recorded in the daily log. On the day of chemotherapy (Day 0), approximately one fourth of the patients could do all of their usual activities (27.7% in the first, and 23.3% in the second cycle). Only a few patients

could do their usual activities on a daily basis during the first 10 days after chemotherapy (11.3% in the first, and 12.8% in the second cycle).

The mean intensity of activities decreased significantly from Day 0 to Day 2 during both cycles (6.0 to 5.5 in the first, and 6.3 to 5.8 in the second cycle) using repeated measures ANOVA ($p = .006$ in the first, and $p = .013$ in the second cycle). The patients' ability to do their usual activities then increased gradually but significantly from Day 2 to Day 10 of each cycle (5.5 to 7.5 in the first, and 5.8 to 7.7 in the second cycle; $p < .001$ for both cycles). These data suggested that patients receiving chemotherapy could perform little more than half of their usual activities on Day 2 of their treatment cycle (Figure 1).

A few women did not rest or nap on the day they received chemotherapy (17.4% in during the first, and 25.9% in the second cycle). Very few patients were able to continue their daily activities without resting during the entire 10 days after the chemotherapy (4.2% in the first, and 8.3% in the second cycle). More than half of the patients who did not rest throughout the treatment period were employed full-time (50% in the first, and 64.7% in the second cycle). Changes in the mean hours of resting corresponded inversely with changes in the mean usual activities score. The mean hours of resting increased significantly ($p < .001$ each cycle) from Day 0 to Day 2 of each cycle (3.3 to 4.2 in the first, and 2.8 to 3.7 in the second cycle). The amount of time these women rested decreased gradually but significantly ($p < .001$ each cycle) from Day 2 to Day 10 of each cycle (4.2 to 1.7 in the first, and 3.7 to 2.0 in the second cycle).

Nausea and Vomiting

Acute nausea was experienced by 46.7% of the patients during the first cycle and by 45.0% of the patients in the second cycle. Delayed nausea occurred in 81.5% of the patients during the first cycle, and in 73.9% of the patients during the second cycle. Acute vomiting was experienced by 15.5% during the first cycle and by 10.0% of the patients in the second cycle. Delayed vomiting occurred in 31.7% during the first cycle and by 28.6% of the patients in the second cycle. The highest incidence rate of nausea was reported on Day 2 of the first cycle (69%), and Day 1 of the second cycle (63.4%). The incidence of vomiting was the highest in Day 0 of the first cycle (24.4%), and Day 1 of the second cycle (27.1%)

The mean acute INVR nausea score for the first cycle was 2.50 ($SD = 3.41$, *range* 0-12, $n = 254$) and 2.37 ($SD = 3.26$, *range* 0-12, $n = 254$) for the second cycle. The mean delayed INVR nausea score for the first data collection period was 16.75 ($SD = 16.77$, *range* 0-101, $n = 255$), and 17.90 ($SD = 20.41$, *range* 0-111, $n = 255$) for the second data collection period. The mean acute INVR vomiting score for the first cycle was 0.82 ($SD = 2.16$, *range* 0-10, $n = 255$) and 0.55 ($SD = 1.77$, *range* 0-11, $n = 255$) for the second cycle. The mean INVR delayed vomiting score for the first data collection period was 2.80 ($SD = 6.05$, *range* 0-48, $n = 254$), and 3.54 ($SD = 9.22$, *range* 0-95, $n = 254$) for the second data collection period (Figure 2). No significant differences were found in acute and delayed nausea and vomiting scores between the first and the second cycle of the chemotherapy.

Functional Status & Nausea/Vomiting

Patterns of change in the INVR nausea score during two cycles of chemotherapy

corresponded with the changes in hours of resting and were inversely related to the changes in usual activities score (Figure 2). Significant relationships among delayed nausea, delayed vomiting, usual activities and hours of resting were found in correlation analyses ($p < .001$) (Tables 4 and 5).

Discussion

The results of this study indicated that the common experience of delayed nausea and the uncommon experience of delayed vomiting are associated with poorer functional status in women undergoing adjuvant chemotherapy for breast cancer. The impact of CINV on functional status has been suggested in prior studies (Farley et al., 1997; O'Brien et al., 1993; Osoba et al., 1997; Palmer, Walsh, McKinna, & Greening, 1980; Rusthoven et al., 1998). It also has been considered that major impact was derived from nausea (Farley et al., 1997; O'Brien et al., 1993; Osoba et al., 1997). Osoba and colleagues (1997) described a group of patients with both nausea and vomiting, either one, or none and found that the group with both nausea and vomiting had significantly worse physical, cognitive, and social functioning, and global quality of life when compared to the group with no nausea and vomiting. Functional status scores of patients who reported vomiting (no nausea) were more like patients who did not experience nausea and vomiting, whereas patients who reported nausea (no vomiting) had functional status change scores that were of an intermediate magnitude between patients without nausea and vomiting and those experiencing nausea and vomiting (Osoba et al., 1997).

In the study by Farley and colleagues (1997) that measured patients 72 hours after chemotherapy, the negative impact on ability to complete usual household tasks was similar for patients with nausea alone and those with both nausea and vomiting. Nausea

also had a significantly greater impact than vomiting on overall functioning, although vomiting was considered to be the major influence in an earlier study without 5-HT₃ antiemetics (O'Brien et al., 1993). Nausea was associated with disruption in most functional status domains at all levels of severity (Osoba et al., 1997). Our study proposed that delayed CINV significantly decreased patients' usual activities and increased hours of resting. The pattern of reduction in usual activities and increase in hours of resting correlates best with delayed, rather than acute chemotherapy induced nausea. Vomiting was not frequently reported by the current study sample and appeared to have less impact on functional status. However, other symptom factors that might bring about change in functional status such as fatigue, depression, sleep, etc. should be controlled in future studies so that the magnitude of the contribution of delayed nausea could be evaluated.

The patterns of CINV obtained in our study correspond with other study results. Two studies reported that the incidence of nausea was highest on Day 1 through 3, and peaked on Day 2 in a sample of patients that had received moderately emetogenic chemotherapy (Rusthoven et al., 1998; Lindley, Bernard, & Fields, 1989). Lindley and colleagues reported this in 1989 before the advent of 5-HT₃ antagonists suggesting that although acute vomiting has decreased; nausea, especially delayed nausea, has not been affected by these drugs. Although Palmer, Walsh, McKinna and Greening (1980) suggested that nausea lasted for 5 days with single agent treatment and for 3 to 5 days when combination therapy was used, the results of our study indicate that nausea lasted for some women at least 10 days after the chemotherapy infusion. This provides additional evidence about the impact of delayed nausea on functional decline in women

receiving chemotherapy. It also suggests that controlling delayed nausea should receive more attention by nurses.

This study has some limitations that must be acknowledged. Data for this study were gathered prior to the release of two new drugs aprepitant (Emend®) and palonosetron (Aloxi®) that are reported to be useful in the treatment of delayed nausea (Cocquyt et al., 2001; Eisenberg et al., 2003; Gralla et al., 2003). To understand the impact of these drugs for women receiving adjuvant chemotherapy for breast cancer, a study should be undertaken. Most of the participants in this study were Caucasian, thus it is difficult to generalize these results to other groups of breast cancer patients. The impact of sedative antiemetics such as prochlorperazine and lorazepam needs further examination in relation to functional status. Other factors that might affect patients' functional status were not tested in this study, thus it is uncertain if delayed nausea and vomiting are the most influential factors in this change in functional status. Although delayed nausea demonstrated a greater impact than delayed vomiting based on patterns of changes, caution should be used in interpreting these results because the magnitude of contribution was not tested.

In conclusion, delayed CINV is associated with patients' functional decline. Delayed nausea should be controlled more vigorously as it prompts a decrease in functional status in women treated with chemotherapy for breast cancer. Perhaps if delayed nausea were better controlled the impact of chemotherapy would be less devastating for women undergoing adjuvant chemotherapy. More research will assist with the answers for these issues.

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Table. 1 Characteristics of the Participants ($N = 303$)

Characteristics	<i>Mean</i>	<i>Standard Deviation</i>	<i>Range</i>
Age, years	51.9	11.0	28-86
Education, years	13.9	2.9	7-23
Time since diagnosis, month*	1.9	1.9	.07-19.4

Characteristics	<i>N</i>	<i>Percent (%)</i>
Relationship status		
Married/Partnered	196	65
Other	105	35
Employed		
Yes	145	48
No	155	52
Retired		
Yes	66	22
No	234	78
Lives alone		
Yes	48	16
No	253	84
Race/Ethnicity		
African-American	28	9
Latina	16	5
White/Caucasian	239	79
Other	18	6
Personal income		
< 20,000	106	42
20,999 - 39,999	79	32
40,000 +	65	26
History of sea sickness		
Yes	72	24
Other	229	76
History of car sickness		
Yes	62	20
Other	240	80
History of morning sickness		
Yes	181	60
Other	121	40
History of nausea with stress		
Yes	67	22
Other	235	78

* Two patients who had recurrence were excluded

Table 2. Treatment Characteristics (*N* = 303)

Characteristics	<i>N</i>	<i>Percent (%)</i>
Type of surgery		
Mastectomy	113	37
Lumpectomy	190	63
Radiation therapy		
Yes	19	7
No	92	33
Planned after chemotherapy	171	61
Adjuvant chemotherapy*		
AC	228	76
CMF	34	11
Other	40	13
Weekly chemotherapy		
Yes	23	7
No	277	93
Prechemotherapy antiemetics		
Dexamethasone	241	80
Ondansetron	148	49
Granisetron	72	24
Dolasetron	51	17
Lorazepam	20	7
Prochlorperazine	12	4
Diphenhydramine	7	2
Prechemotherapy antiemetics changed		
Yes	18	6
No	282	94
Postchemotherapy oral antiemetics		
Prochlorperazine	211	70
Ondansetron	113	38
Dexamethasone	68	23
Lorazepam	59	20
Granisetron	36	12
Promethazine	15	5
Diphenhydramine	15	5
Postchemotherapy oral antiemetics changed		
Yes	24	8
No	273	92

Table 3. Changes in Functional Status (SF-36 Scales)
after Two Cycles of Chemotherapy

SF-36 Scale	Before	After	<i>p</i>
Physical functioning	78.57 ± 22.54	71.43 ± 23.30	<.001
Role-physical	38.75 ± 43.33	30.61 ± 39.02	.003
Bodily pain	57.36 ± 24.35	73.34 ± 25.29	<.001
General health	72.17 ± 18.15	70.00 ± 18.52	.029
Vitality	54.33 ± 22.30	47.51 ± 22.19	<.001
Social functioning	70.99 ± 23.97	65.83 ± 24.04	.001
Role-emotional	64.97 ± 42.57	65.36 ± 43.65	.893
Mental health	71.23 ± 17.22	74.86 ± 17.12	<.001

Table 4. Correlations among Nausea, Vomiting, Usual Activities, and Hours of Resting in the First Cycle

	Acute Nausea	Acute Vomiting	Delayed Nausea	Delayed Vomiting
Day 0 Usual Activities	-.101 (.113)	.001 (.993)	-.043 (.497)	-.126* (.048)
Day 0 Hours of Resting	.022 (.737)	-.073 (.261)	.006 (.932)	.027 (.674)
Days 1-10 Usual Activities	-.265** ($<.001$)	-.163* (.012)	-.344** ($<.001$)	-.318** ($<.001$)
Days 1-10 Hours of Resting	.235** (.001)	.193** (.005)	.329** ($<.001$)	.466** ($<.001$)

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

Table 5. Correlations among Nausea, Vomiting, Usual Activities, and Hours of Resting in the Second Cycle

	Acute Nausea	Acute Vomiting	Delayed Nausea	Delayed Vomiting
Day 0 Usual Activities	-.080 (.238)	.020 (.764)	-.109 (.105)	-.040 (.558)
Day 0 Hours of Resting	.020 (.775)	-.001 (.992)	.130 (.055)	.079 (.245)
Days 1-10 Usual Activities	-.261** ($<.001$)	-.186** (.004)	-.510** ($<.001$)	-.451** ($<.001$)
Days 1-10 Hours of Resting	.250** ($<.001$)	.313** ($<.001$)	.409** ($<.001$)	.542** ($<.001$)

** Correlation is significant at the 0.01 level (2-tailed)

Figure 1. Usual Activities and Hours of Resting over Time

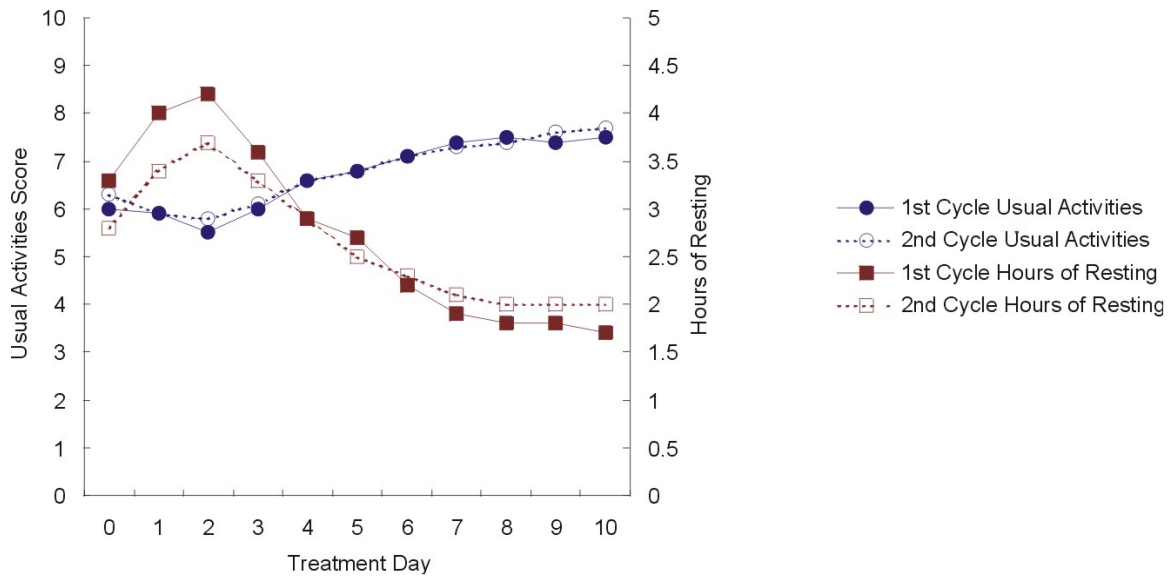
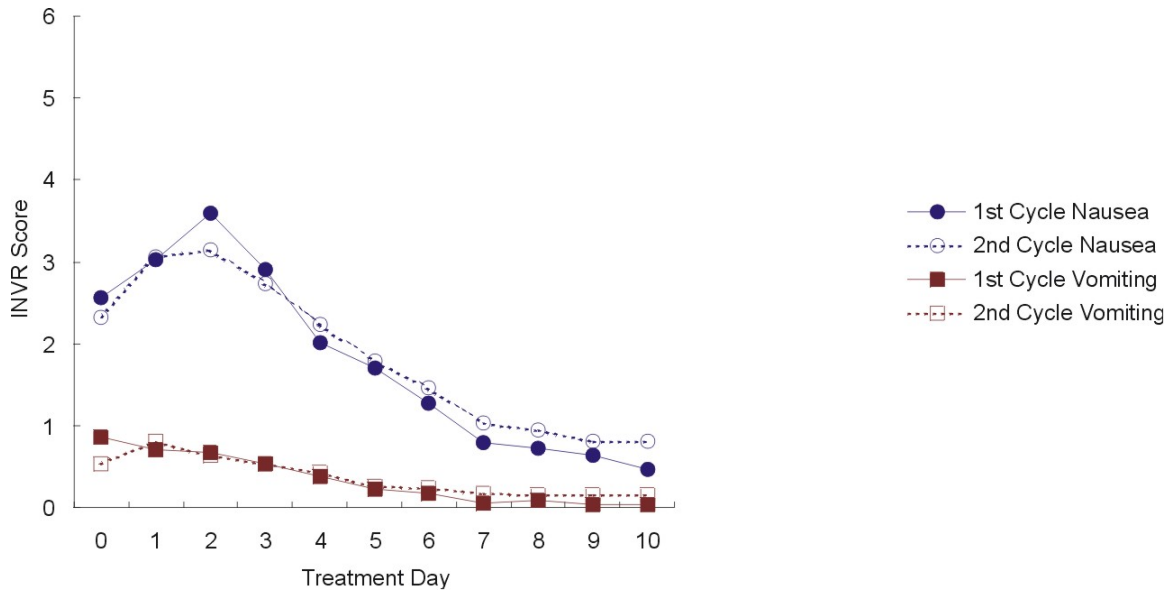


Figure 2. Nausea and Vomiting over Time



Summary

The control of chemotherapy-induced nausea and vomiting (CINV) is a moving target as the entire mechanism is still unclear, and the control of symptoms is not satisfactory. Chemotherapy-induced nausea (CIN) was a common and challenging symptom whereas chemotherapy-induced vomiting was less common experience as presented in chapter 2 and 4. Nausea lasted an average of eight days after the chemotherapy in the study in chapter 2. Some patients experienced nausea until 11 days after chemotherapy in the studies in chapter 2 and 4. Even after completion of the chemotherapy, nausea was still an issue among some of the breast cancer patients as described in the study in chapter 3. The pattern of changes in nausea intensity was unique among breast cancer patients receiving moderate to highly emetogenic chemotherapy that had the peak nausea level after two days from chemotherapy administration (day 3 in chapter 2, and Day 2 in chapter 4) as presented in chapter 2 and 4.

Delayed nausea as well as vomiting had a significant inverse relationship with the functional status of patients as measured by usual activity and hours of resting, whereas acute nausea and vomiting was not related to the patients' functional status in the study in chapter 4. Specifically, the pattern of change in delayed nausea (not delayed vomiting) corresponded with the change in hours of resting and inversely with usual activities although the magnitude of the relationship was not evaluated. Another interesting finding was that delayed nausea, especially after the peak levels of nausea on day 3 had a significant relationship with the frequency of P6 digital acupressure in the study presented in chapter 2. Delayed nausea should be considered as an important topic for future studies of CINV.

However, it is meaningful to remind researchers about the relationship between acute and delayed symptoms. The influence of acute symptoms to the delayed symptoms has been reported in several studies (Italian Group for Antiemetic Research, 1994, 1997, 2000). In the study in chapter 2, the relationship of acute nausea to the delayed nausea was demonstrated again as those patients who used more frequent acupressure after three days from chemotherapy administration (day 4) were the ones whose acute nausea was more intense than others. The importance of controlling acute nausea was emphasized as the initial difference in nausea intensity continued throughout the 11 days after chemotherapy. The balanced control of symptoms throughout acute and delayed phases is in need of further research.

Two interventions that could be used in addition to antiemetics were investigated to improve the control of CINV. The first intervention was P6 acupressure which had been recognized as an effective intervention for CINV control. However, the review of literature about acupressure studies in chapter 1 that included ten controlled acupressure studies reported that the overall effect of P6 acupressure in CINV control was strongly suggestive but not conclusive. The result of acupressure wrist bands studies were varied study by study, whereas digital acupressure studies all supported the effect of acupressure. A meta-analysis of acupressure studies supported its effect in acute nausea control whereas a recently published three-arm randomized controlled trial supported an acupressure effect in delayed nausea and vomiting control. Overall, the evaluation of a P6 acupressure effect was not straightforward as it was unknown whether the two acupressure modalities, acupressure wrist band and digital acupressure were comparable. There were other components such as predisposing factors of CINV, as well as use of

antiemetics that could have confounded the evaluation of acupressure effects. The characteristics of participants such as diagnosis and ethnicity had limited generalizability of the study. For a future acupressure study, controlling the aforementioned possibly confounding components by study design and considering generalizability of the study result will help evaluate the acupressure effect with more confidence.

The actual acupressure frequency was reported as an average of twice per day during the 11 days after chemotherapy among breast cancer patients when patients were instructed to apply once daily mandatory acupressure plus additional acupressure when needed in the study in chapter 2. Acupressure was applied most frequently on day 3 when the intensity of nausea was at peak. However, the actual frequency of acupressure depended upon individual needs as some patients did not use acupressure whereas some patients used acupressure eight times on day 3. In general, participants who used more acupressure were the ones who had experienced more intense nausea as was expected by the study protocol, which instructed participants to use additional acupressure whenever nausea occurred.

The second intervention was an aerobic exercise which effect on CINV control had been inconsistent in prior studies. Breast cancer patients who undertook a moderate level of aerobic exercise, for a minimum of 20 minutes per session three times a week, during cancer treatment experienced significantly less nausea at the completion of adjuvant cancer treatment as presented in chapter 3. A significant difference in nausea intensity at the completion of adjuvant cancer treatment and a decrease in nausea intensity to the level that could be interpreted as having no nausea suggested an effect of exercise on nausea control even with a concern of low average nausea intensity in this

study. This exercise trial evaluating actual exercise performance and its relationship to nausea was also limited by a small sample size and requires further investigation to examine exercise's effect on chemotherapy-induced nausea control during chemotherapy.

The results of this dissertation project provide a number of implications for CINV management. Three minutes of once daily mandatory acupressure and additional acupressure as needed is the recommended acupressure instruction for clinical application and also for any future acupressure trial based on current evidence. Achieving better control of the symptom with an average of two times of daily acupressure application as in the study in chapter 2 could be informative for patients who are instructed to apply acupressure as their additional intervention for CINV. Moderate levels of aerobic exercise, for a minimum of 20 minutes per session three times a week, could be suggested as a potential intervention for nausea control. The inverse relationship between delayed nausea and vomiting to the patient's functional status calls for expanding the attention of care from just symptom management to the impact of the symptom on the lives of patients.

This dissertation project also suggests further study needs and future study questions with regards to CINV management. P6 acupressure needs to be investigated further to achieve more confident conclusions about its effect on CINV control. Unique features of CINV, such as the symptom having acute and delayed phases and the duration of symptom experiences for up to 11 days after chemotherapy, need to be included in the study design. Predisposing factors of CINV as well as the antiemetic use also need to be controlled. A comparison study evaluating the use of acupressure band versus digital acupressure in CINV control will help understanding some of the incongruent results

from the reported acupressure trials. Employing both a sham and a true control group in an acupressure study will help discriminate a true acupressure effect between the placebo and the control group. Once the P6 acupressure effect on CINV control in one subpopulation, such as female breast cancer patients, is established, the acupressure trial could be expanded and the acupressure effect could be evaluated more comprehensively among more diverse groups of patients.

Although the benefit of a customized application of acupressure was supported by the study in chapter 2, it is also questionable whether using other acupressure protocols, such as using acupressure only when needed or using more frequent mandatory acupressure plus allowing additional acupressure as needed, would make the control of the symptom different. To evaluate the influence of the different frequencies of acupressure, a future study needs to include several acupressure protocol arms.

Further exercise studies during chemotherapy are also recommended to evaluate the effect of a moderate level of aerobic exercise on controlling CINV during chemotherapy.

Studies about known and potential predisposing factors of CINV are required. Although comprehensive analysis of the predisposing factors was not available in the study in chapter 2 because of limitations due to a small sample size, only age had significant inverse relationship with nausea among the reported predisposing factors of CINV. BMI is not a known predisposing factor but it also had an inverse relationship with nausea. It is also questionable as to which other known predisposing factors of CINV such as nausea with pregnancy and a history of motion sickness, or possible predisposing factor such as BMI are really the factors that influence CINV. In future

intervention studies, predisposing factors could be controlled to interpret the effect of the interventions with more confidence.

The impact of CINV on functional status could be evaluated when the study is designed to have different intervention arms that would provide different levels of symptom control. When the control of CINV during chemotherapy and the change in functional status after completion of chemotherapy would show significant relationship, the impact of CINV on functional status could be more supported. Investigation of concurrent symptoms will help understand the true impact of CINV as other symptoms that could be associated with chemotherapy might influence the functional status of the patients.

In conclusion, CINV, especially in the delayed phase, and nausea are important clinical issues that may have influence on functional status of patients. The use of P6 acupressure and performing a moderate level of aerobic exercise are suggested for CINV control, however, further study is clearly needed. In future CINV and its intervention studies, it is imperative to consider important design and methodological issues which were suggested through this dissertation project.

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