The Relationship of Chemotherapy-Induced Nausea to the Frequency of Pericardium 6 Digital Acupressure

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Purpose/Objectives: To explain the relationship between the intensity of chemotherapy-induced nausea (CIN) and the frequency of pericardium 6 (P6) digital acupressure.

Design: Secondary data analysis of a multicenter, longitudinal, randomized, clinical trial.

Setting: Nine community clinical oncology programs and six independent sites in the United States.

Sample: 53 patients with breast cancer who received moderate to highly emetogenic chemotherapy and applied P6 digital acupressure in addition to antiemetics to control CIN.

Methods: A daily log measuring nausea intensity and the frequency of acupressure for 11 days after the administration of chemotherapy. Hierarchical generalized linear modeling procedure (multilevel negative binomial regression) was used for analyzing the data.

Main Research Variables: Nausea intensity and acupressure frequency.

Findings: Participants used acupressure an average of two times per day (SD = 1.84, range 0–10). Women who used acupressure more frequently after the peak of nausea (on day 4) were predicted to have a 0.97-point higher nausea intensity in the acute phase than women who used acupressure less frequently, controlling for the effects of other variables in the model (incidence rate ratio = 1.52, $p < 0.01$).

Conclusions: Patients with breast cancer whose nausea intensity started higher from the acute phase continued to experience higher symptom intensity during the 11 days after chemotherapy administration and required more frequent acupressure even after the peak of nausea.

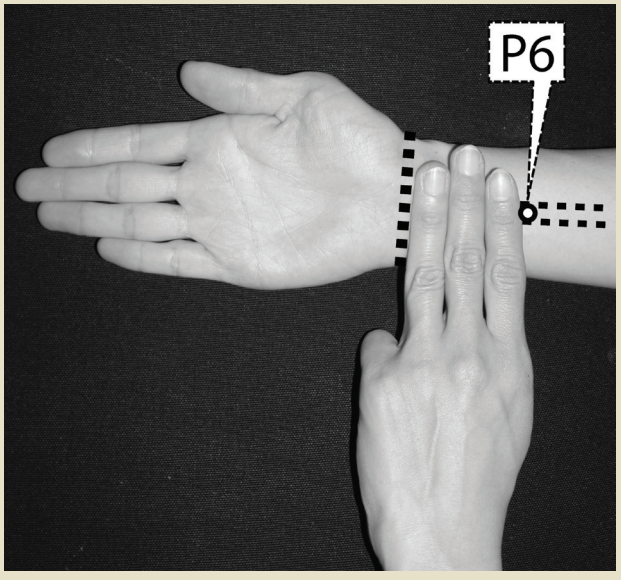
Implications for Nursing: Careful assessment and management of acute CIN with continuous monitoring and care of CIN in the delayed phase are important nursing issues in caring for patients receiving chemotherapy.

The American Cancer Society (2010) estimated that 1,529,560 new cases of cancer will be diagnosed in 2010 and 80% will be treated with chemotherapy (Massaro & Lenz, 2005). This translates to more than 1 million patients undergoing chemotherapy. Chemotherapy-induced nausea (CIN) has been rated as the most distressing side effect of chemotherapy (de Boer-Dennert et al., 1997; Griffin et al., 1996; Rhodes & McDaniel, 2001). In a study by Molassiotis et al. (2008) of 102 patients with diverse cancer diagnoses, about 71% had acute nausea, which was defined as nausea within 24 hours after chemotherapy administration (Navari, 2003), and about 60% experienced delayed nausea, defined as nausea that begins and persists for more than 16–24 hours after chemotherapy (Lindley et al., 2005), when highly emetogenic chemotherapy and routine antiemetics were administered. With moderately emetogenic chemotherapy and routine antiemetics, about 47% had acute nausea and about 61% experienced delayed nausea (Molassiotis et al., 2008). Even when patients were treated for moderately emetogenic chemotherapy with a 5-hydroxytryptamine 3 receptor antagonist (5-HT_3 RA) (e.g., palonosetron), a neurokinin-1 receptor antagonist (NK-_1 RA) (e.g., 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-HT_3 RAs include headaches, dizziness, constipation, and diarrhea (Kovac, 2003). Adverse effects of NK-_1 RAs include asthenia and fatigue (Dando & Perry, 2004). In addition, 5-HT_3 RAs and NK-_1 RAs are expensive. Finding more cost-effective nausea control modalities with fewer adverse effects for additional CIN control is desirable.

The effect of pericardium 6 (P6) 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, Williams, & Sergiou, 1992; Roscoe et al., 2003, 2006) and one quasi-experimental (Shin, Kim, Shin, & Juon, 2004) clinical trials as well as in one meta-analysis (Ezzo et al., 2005). Traditional Chinese medicine postulates illness as disharmony of the vital energy of the body, qi. Acupressure helps qi resume its balance (Kaptchuk, 2002; Liangyue et al., 1987; Shanghai College of Traditional Medicine, 1981; Stux & Pomeranz, 2003). The P6 acupressure point 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) (see Figure 1). In the studies of P6 digital acupressure, pressure at P6 was applied for 3–5 minutes 1–3 times daily for at least five days over one cycle of chemotherapy (Dibble et al., 2000, 2007; Shin et al., 2004). The actual frequency of acupressure in these studies could have ranged from none to several applications per day because each study allowed additional application of acupressure as needed. How frequently patients applied acupressure to achieve CIN control and whether the intensity of CIN had any relationship with the frequency of acupressure is unknown.

The purpose of the current study is to explain the relationship between the intensity of CIN and the frequency of P6 digital acupressure in a group of patients with breast cancer who received moderate to highly emetogenic chemotherapy and applied P6 digital acupressure as an additional intervention for CIN control. The antiemetic therapy ordered for the women to control their CIN was that of the healthcare providers' choice.



Note. The P6 acupressure point is located approximately three finger-widths up from the first wrist crease and between two tendons.

Figure 1. Pericardium 6 (P6) Acupressure Point

Note. Image courtesy of Jiyeon Lee. Used with permission.

Methods

Design

This study is a secondary data analysis of a multicenter, longitudinal, randomized, clinical trial that compared differences in chemotherapy-induced nausea and vomiting among three groups (P6 digital acupressure, placebo digital acupressure, and usual care) and found P6 digital acupressure effective in controlling delayed chemotherapy-induced nausea and vomiting in women undergoing chemotherapy for breast cancer. In the parent study, participants were instructed to perform digital acupressure for three minutes or point release (i.e., until mild discomfort or pain caused by acupressure diminished when the point was held long enough) at the P6 points on both arms in the morning, and an additional three minutes of acupressure to one arm whenever nausea occurred (Dibble et al., 2007; Gach, 1990).

Sample

The current study included 53 women who were randomly assigned to the P6 digital acupressure group in the parent study. Participants in the parent study were recruited from nine community clinical oncology programs associated with the University of Texas M.D. Anderson Cancer Center and six independent sites located throughout the United States. Inclusion criteria were 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, 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), women who were beginning their second or third cycle of chemotherapy, women who were able to communicate in English (both verbally and in writing), and 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 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 at the time of treatment and for home use.

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 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 et al., 2000, 2007; Lee, Dibble, Pickett, & Luce, 2005). Acupressure use was measured by the frequency of P6 digital acupressure. The daily logs for the 11 days after chemotherapy were used for the current study.

Analytic Approaches

Hierarchical generalized linear model (HGLM), in particular, multilevel negative binomial regression, was used to predict changes in the intensity of CIN in relation to the frequency of P6 digital acupressure over the 11 days following chemotherapy. The influence of predisposing factors for CIN also was tested through HGLM. Correlation analysis was used to examine association between two different measures of nausea intensity (NRS and INVR). Statistical software (SPSS® [v.14.0] for Microsoft® Windows® and STATA 10 SE) was used to analyze data.

Results

Demographics

Fifty-three women with breast cancer ($\bar{X}$ age = 49, SD = 10.55, range 27–74) were included in this study. Eighty-one percent of the women were Caucasian and 72% were married. On average, participants had 14.7 years of education and 42% of them were employed. Overall, participants were overweight with a mean body mass index of 27.31 (SD = 5.18, range 18.09–43.89). Eighty-one percent had a diagnosis of ductal carcinoma and 15% had lobular breast cancer. Forty-nine percent were treated with mastectomy and 47% with lumpectomy. Seventy-four percent of the women underwent nodal dissection and 74% were treated with cyclophosphamide and anthracycline, 13% received 5-fluorouracil with anthracycline, and 9% received a taxane with anthracycline (two participants, 4%, did not provide data). Four participants received radiation therapy as a part of their treatment. To evaluate initial control of CIN with antiemetics, the use of antiemetics was compared to the National Comprehensive Cancer Network ([NCCN], 2008) antiemetic guidelines rather than assessing adherence of antiemetic guidelines at the time of study conduction.

The antiemetic guidelines reflect scientific and clinical understanding about the mechanisms of CIN and help evaluate the initial control of CIN achieved by antiemetics. Eight participants received aprepitant as their antiemetic, and no participants received antiemetics as outlined in the NCCN antiemetic guidelines for highly emetogenic chemotherapy. When antiemetic use was compared to the NCCN antiemetic guideline for moderately emetogenic chemotherapy, 72% of the women received recommended antiemetics in the acute phase; however, only 26% received recommended antiemetics for the delayed phase.

Chemotherapy-Induced Nausea

All 45 participants (85% of the 53 total participants) who provided daily records of the intensity 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 intensity on day 11 was excluded from the analysis as the participant was considered an outlier. The results from the nausea intensity ratings are presented in this study because the nausea intensity ratings from the NRS were highly correlated with the INVR nausea scores (r = 0.92, $p < 0.01$) and the results from HGLM analyses corresponded to each other.

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 ($\bar{X}$ = 4.93, SD = 2.57, range 0–10). The nausea intensity increased from days 1–3 and decreased after that time. On average, the participants experienced nausea up to day 7, and stopped having the symptom from day 8 onward ($\bar{X}$ = 7.93, SD = 2.72, range 1–11). Participants used antiemetics up to day 6 and stopped using antiemetics from day 7 ($\bar{X}$ = 7, SD = 2.85, range 1–11). The largest proportion of patients stopped using antiemetics on day 5 (n = 9) (see Figure 2).

Pericardium 6 Digital Acupressure Frequency

The average amount of acupressure use over 11 days was two times per day ($\bar{X}$ = 1.9, SD = 1.84, range 0–10).

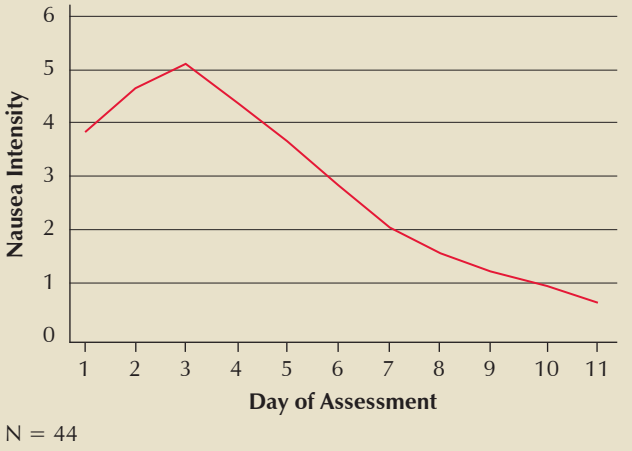


Figure 2. Mean Predicted Value of Nausea Intensity Through the Hierarchical Generalized Linear Model

Participants used acupressure for an average of seven days after chemotherapy ($\bar{X}$ = 7.47, SD = 3.23, range 1–11). The most frequent application of acupressure was on day 3. Throughout day 3, 12 participants applied acupressure more than five times per day (the largest number of participants who used more than five acupressure treatments per day during the 11 days), 16 participants used acupressure 3–4 times per day, and 10 participants used acupressure 1–2 times per day. Four participants did not use any acupressure on day 3 (one did not have nausea and did not use any antiemetics). Three scored their nausea intensity at 3, 5, and 8, respectively. Among the three, two received antiemetics according to the NCCN antiemetic guideline for moderately emetogenic chemotherapy for the acute phase but not during the delayed phase (see Table 1).

Chemotherapy-Induced Nausea in Relation to the Pericardium 6 Digital Acupressure Frequency

A HGLM analysis suggested that a significant change occurred in nausea intensity ratings depending on the time after chemotherapy infusion, controlling for the effects of other variables in the model. The model predicted that a 0.73-point increase would occur in the nausea intensity ratings (0–10) with each day after chemotherapy from days 1–3 (incidence rate ratio [IRR] = 1.25, p = 0.02). A 1.22-point decrease in nausea intensity ratings did occur from days 4–11 (IRR = 0.58, p < 0.01). Participants who experienced more intense nausea used acupressure more frequently during the acute phase (day 1), as predicted by the study protocol (participants were instructed to use additional acupressure whenever nausea occurred). Women who used acupressure more frequently (one more application of acupressure) were predicted to have a 0.33-point (IRR = 1.12, p = 0.01) higher nausea intensity rating in the acute phase than women who used acupressure less frequently. The increase in nausea intensity ratings from days 1–3 was not associated with the frequency of the acupressure (IRR = 0.96, p = 0.2). However, the decrease in nausea intensity ratings from days 4–11 was associated with the frequency of the acupressure, controlling for the effects of other variables in the model (IRR = 1.11, p < 0.01). The results suggest that the nausea intensity in the acute phase has a significant relationship to the frequency of acupressure as expected by the study protocol. The changes in nausea intensity from days 4–11 are significantly related to the frequency of acupressure. When a graph was drawn to compare the predicted value of nausea intensity in relation to the acupressure frequency through the HGLM, women who experienced more intense nausea used more frequent acupressure over 11 days after chemotherapy and a different pattern of change in nausea intensity was observed during days 4–11 among women who used acupressure more than five times per day (see Figure 3).

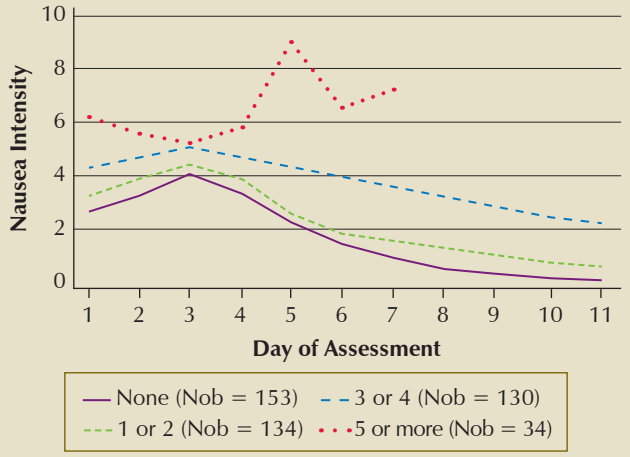
An issue arose in interpreting the results because the line in the graph represented the mean nausea intensity of a group of participants whose acupressure frequency was similar on a specific day. A group of participants who belonged to one acupressure frequency category changed depending on the day after chemotherapy. Because the acupressure frequency had made a significant contribution to the change in nausea intensity ratings during days 4–11 (after the peak of nausea), acupressure frequency for this period was reviewed. An interesting pattern was noted in participants who used acupressure more than five times during the period (days 4–11) because they were the ones who used acupressure more than five times on day 4. Participants were recategorized 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. Women who used acupressure more than five times on day 4 experienced highest nausea intensity over 11 days, and their peak of nausea intensity was different from the other groups (see Figure 4).

A HGLM analysis with the new categorization of the participants according to the acupressure frequency on day 4 also showed significant changes in nausea intensity depending on the length of time after chemotherapy infusion, controlling for the effects of other variables in the model (n = 42). The model predicted a 0.47-point increase in the nausea intensity with each additional day after chemotherapy from days 1–3 (IRR = 1.25, p < 0.01). A 0.71-point decrease in nausea intensity also was noted from days 4–11 (IRR = 0.63, p < 0.01). Women who used acupressure more frequently on day 4 (one level higher in the acupressure frequency category) were predicted to have 0.97-point higher acute nausea intensity than women who used acupressure less frequently, controlling for the effects of other variables in the model (IRR = 1.52, p < 0.01). Acupressure

Table 1. Acupressure Frequency

Day	$\bar{X}$	SD	Range
1	2.18	1.53	0–8
2	3.28	2.15	0–10
3	3.32	1.92	0–8
4	2.69	1.73	0–6
5	2.3	1.91	0–9
6	1.8	1.58	0–6
7	1.39	1.41	0–6
8	1.23	1.33	0–4
9	0.88	1.35	0–4
10	0.78	1.21	0–4
11	0.79	1.22	0–4

N = 44



Nob—number of observations

Figure 3. Mean Predicted Value of Nausea Intensity by Four Categories of Acupressure Frequency

frequency on day 4 was not associated with change in nausea intensity over 11 days after chemotherapy. Results were interpreted as women who used more frequent acupressure on day 4 had higher levels of nausea intensity from the acute phase and continued to experience higher levels of nausea intensity over 11 days. A graphic difference observed in Figure 4 about different peak of nausea intensity among those who used acupressure more than five times on day 4 was not supported in the HGLM analysis (see Figure 5).

Predisposing Factors

A HGLM analysis was conducted regarding predisposing factors for nausea. Because the total sample was limited in size, each factor (age, motion sickness, morning sickness, and nausea with stress) was entered into the HGLM model that analyzed CIN change in relation to the frequency of acupressure. Age was the only significant predisposing factor for nausea intensity in acute phase, although the change was small, controlling for the effects of other variables in the model. With each year increase in age, the model predicted a 0.35-point decrease in nausea intensity ratings (IRR = 0.97, $p < 0.01$). Age also was significantly associated with the nausea intensity ratings when the participants were recategorized into four groups according to the frequency of acupressure applied on day 4 (IRR = 0.97, $p < 0.01$).

Discussion

This study is the first that reports CIN intensity change over 11 days in relation to the frequency of P6 digital acupressure. The pattern of nausea intensity change found in this study with the peak nausea on day 3 corresponds with the results from studies with middle-aged, mostly Caucasian, women patients with breast cancer (Dibble et al., 2000; Lee et al., 2005; Molassiotis et al., 2007). The influence of acute nausea on delayed nausea that was proposed by this study also had been supported in other studies (Italian Group for Antiemetic Research, 1994, 1997, 2000).

This study demonstrated how participants actually applied acupressure after they received instructions to perform mandatory once daily acupressure and use additional acupressure as needed. Improved CIN control by using an average of two P6 acupressure applications over 11 days after chemotherapy provides helpful information when introducing P6 acupressure to patients expecting chemotherapy. On average, participants used acupressure for one more day after they had stopped taking antiemetics. This proposes a value of acupressure in the delayed phase as participants need to control their symptoms when antiemetic use is not necessary or when antiemetics are discontinued because of side effects.

Given that the P6 acupressure group achieved better control of CIN in the parent study, observing different acupressure needs among patients in the P6 acupressure group is of interest. The efficacy of the acupressure protocol that allowed additional acupressure was supported because patients had different acupressure needs. Additional study is recommended to understand the different needs for acupressure frequency. Genetic predisposition or diagnosis of the participants according to traditional Chinese medicine theory might lend some insights about the use of acupressure for CIN. Whether applying more frequent mandatory acupressure would improve CIN control is questionable.

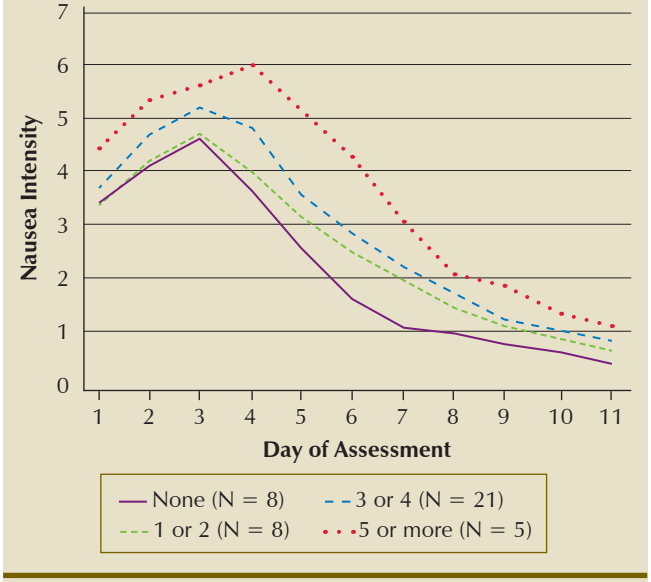


Figure 4. Mean Predicted Value of Nausea Intensity Based on Day 4 Acupressure Frequency

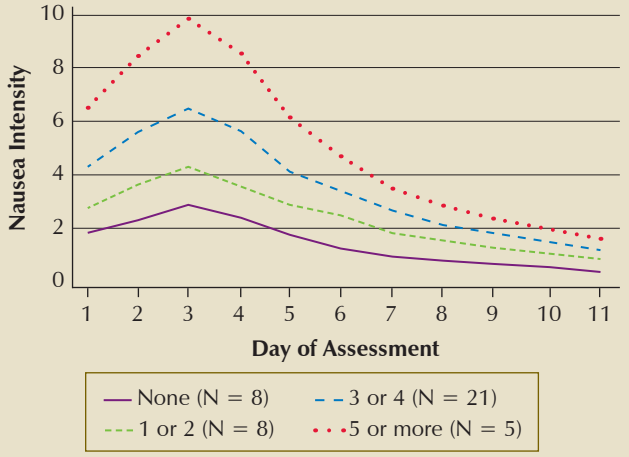


Figure 5. Mean Predicted Value of Nausea Intensity: Four-Category Acupressure Frequency on Day 4 Variable Into Hierarchical Generalized Linear Model

A future study should include multiple acupressure protocol groups to evaluate the influence of different frequency of mandatory acupressure in CIN control.

Although using antiemetics of the provider's choice reflected usual practice among clinicians, no control over antiemetic use is one of the limitations of this study. Only eight participants received aprepitant as their antiemetic, partly because aprepitant was released toward the end of the parent study. No participant received antiemetics that were recommended in the NCCN antiemetic guideline for highly emetogenic chemotherapy (5-HT_3 RAs, $NK\text{-}_1$ RAs, and dexamethasone in the acute phase, $NK\text{-}_1$ RAs for days 2–3, and dexamethasone for days 2–4) (NCCN, 2008). Whether or not acupressure can contribute to additional control of CIN with antiemetics that are recommended by antiemetic guidelines for highly emetogenic chemotherapy is a question for further exploration. No acupressure trials that used acupressure in conjunction with strict adherence to the published antiemetic guidelines could be located in the literature. Strict control of antiemetic use in acupressure trials will help to establish the symptom relief that can be achieved with acupressure. When an antiemetic regimen is controlled and the antiemetic use is tracked, one interesting question is whether additional acupressure could decrease antiemetic use. However, not all clinicians routinely adhere to the antiemetic guidelines in their practice, cost of antiemetics are expensive, and the antiemetic guidelines are mainly for vomiting control and are less effective in nausea control (Herrstedt, 2008).

Age was found to be the only contributing predisposing factor to the differences in acute nausea intensity, although additional 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 (Booth et al., 2007; Dibble et al., 2007; Dodd, Onishi, Dibble, & Larson, 1996; Roila et al., 1985, 1989). However, the cutoff point for young or old age needs further investigation because studies used different cutoff points in comparing age groups. The current study did not stratify participants into different age groups in analyzing the relationship of age and CIN.

A relatively small sample size limited analysis of predisposing factors and the generalizability of this study. Although day 4 acupressure frequency had an interesting relationship with acupressure use during days 4–11 (after the peak of nausea) and had a significant relationship with nausea intensity in the acute phase, the relationships could be confined to this study sample and not be replicated among different, larger groups of patients. This study also had the issue of missing data in relation to longitudinal data collection that resulted in various sample size among analyses.

Conclusion

This study suggests an interesting relationship between nausea intensity and acupressure frequency. Women with breast cancer who required more frequent acupressure even after the peak of nausea (on day 4) were the ones whose acute nausea was more intense than the others. The initial difference in nausea intensity continued throughout the 11 days following chemotherapy. Careful assessment and management of acute CIN with continuous monitoring and care of delayed CIN are considered essential for the care of patients receiving chemotherapy. Different acupressure needs among patients on each day after chemotherapy supports the efficacy of an acupressure protocol that allows additional acupressure to the mandatory amount. A future study regarding CIN and the frequency of P6 digital acupressure with a large number of participants and multiple acupressure protocols is recommended to further investigate the relationship between CIN and acupressure frequency.

Jiyeon Lee, RN, PhD, is a clinical instructor, and Suzanne Dibble, RN, DNSc, and Marylin Dodd, RN, PhD, FAAN, both are professor emerita, all in the School of Nursing, Donald Abrams, MD, is a professor in the School of Medicine, and Beverly Burns, LAc, MS, is an acupuncturist at the Osher Center for Integrative Medicine, all at the University of California, San Francisco. The parent study was funded by the National Cancer Institute (RO1-84014) and the Community Clinical Oncology Program (U10 CA 045809-15). This study was supported by the University of California, San Francisco, Graduate Student Research Award and the University of California, San Francisco, School of Nursing Century Club Award. Lee can be reached at jiyeonest@hotmail.com, with copy to editor at ONFEditor@ons.org. (Submitted September 2008. Accepted for publication November 12, 2009.)

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