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Acupressure for chemotherapy-induced nausea and vomiting in breast cancer patients: a multicenter, randomised, double-blind, placebo-controlled clinical trial

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Dedication

Dedicated to-------

My parents and all my familly with consistant love

Acknowledgment

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My deep appreciation goes to my parents, brothers, and sisters for their encouragements and support.

"إقـــــــرار"

أنا الموقع أدناه مقدم الرسالة التي تحمل العنوان:

مدى تأثير ألأساور الضاغطة في منع القيء والغثيان عند مريضات

سرطان الثدي واللواتي يخضعن للعلاج الكيماوي

Acupressure for chemotherapy-induced nausea and vomiting in breast cancer patients: a multicenter, randomised, double-blind, placebo-controlled clinical trial

أُقرّ بأن ما اشتملت عليه هذه الرسالة، إنّما هو نتاج جهدي الخاصّ، باستثناء ما تمّت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككلّ أو أيّ جزء منها، لم تُقدّم من قبل لنيل أيّة درجة أو لقب علميّ أو بحثيّ لدى أيّة مؤسسة تعليميّة أو بحثيّة أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: اسم الطالب:

Signature: ---------- التوقيـــع

Date: التاريـــخ:

ACRONYMS

5HT	5 Hydroxy Tryptamine (serotonin)
5-HT_3	5-hydroxytryptamine 3
NK_1 receptor	Neurokinin1-Receptor
NV	Nausea & Vomiting
5-HIAA	5-hydroxyindoleacetic acid
NTS	Nucleus Tractus Solitarius
CINV	Chemotherapy-Induced Nausea and Vomiting
CIV	Chemotherapy Induced Vomiting
CSF	Cerebro Spinal Fluids
QOL	Quality of Life
ANS	Autonomic Nervous System
MOH	Ministry of Health
TENS	Transcutaneous Electrical Nerve Stimulator
ASCO	The American Society of Clinical Oncology
TCM	Traditional Chinese Medicine

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Abstract

Purpose: To examine the efficacy of P6-acupressure in preventing chemotherapy- induced nausea and emesis associated with highly emetogenic chemotherapy (i.e. doxorubicin as adjuncts to standard 5-HT_3 receptor antagonist (granisetron) and dexamethasone as antiemetic given as part of routine care in reducing acute nausea (during the day of treatment) and delayed nausea (2-5 days) following the day of chemotherapy. The second aim is to examine the efficacy of the acupressure bands with stimulation of P6 in reducing vomiting and in maintaining Quality of Life (QOL).

Patients and methods: A randomized, double-blind, placebo controlled trial. One group received acupressure with bilateral stimulation of P6 (n=42), a second group received bilateral placebo stimulation, (n=42) and a third group received no acupressure wrist band and served as a control group, (n=42). Acupressure was applied using a Sea-Band (Sea- Band UK Ltd., Leicestershire, England) that patients to wear for the 5 days following the chemotherapy administration. Assessments of acute and delayed nausea and emesis, quality of life(OOL), patients' satisfaction, recommendation of treatment and requirement of rescue antiemetic were obtained.

Results: Significant difference was found in the severity of early nausea >3 (0-6 scale) in the acupressure group M (SD) 1.62 (2.04) as compared to placebo group 2.17 (2.09), p=0.0006.

Astatically significant decrease was found with the proportion of patients who had a moderate to very sever nausea 24hs following chemotherapy>3(0-6) scale in the acupressure group,43%(18/42)as compared to placebo group,67%(28/42), p=.0284. Table 4.3

The acupressure group had a statistically significant reduction in the incidence of delayed nausea 40% (17/42) as compared to the control group 62% (26/42) (p= 0.0495). Further analyses indicated that significant difference existed in the intensity of delayed nausea by acupressure group M (SD) 1.45 (1.73), p= 0.0002 as compared to control 2.03 (1.91). Significant difference also existed in the intensity of delayed nausea by placebo group 1.33 (1.66), p= 0.0010 as compared to control 2.03 (1.91). Here a placebo effect was noted.

Astatically significant decrease was found with the proportion of patients who had a moderate to very sever nausea days 2-5 >3(0-6) scale, in the acupressure group,55%(23/42),(p=0.0206),and in the placebo group52% (22/42), p= 0.0116,as compared to the control group79% (33/42). Aplacebo effect was noted.

The mean number of delayed emetic episodes days 2-5 was significally less in the acupressure groupM(SD) 2.7(1.87) as compared to placebo 3.3(1.9), p= 0.0022 and control group 2.07(1.20), p= 0.0005

Requirement of rescue antiemetic was significantly lower in P6-acupressure (55%, 23/42), as compared to control group (76%, 32/42) (p= 0.0389).

Eight one percent (35/42) of the patients in acupressure group were significantly satisfied with P6-acupressure as compared to placebo group 64% (27/42), p= 0.0471. Seventy nine percent (34/42) of the patients in acupressure group would recommend P6-acupressure to another patients as compared to placebo group 62% (26/42), p= 0.0533 .

CONCLUSIONS: P-6 Acupressure is efficacious for the control of delayed chemotherapy induced nausea and emesis and is a value-added method in addition to pharmaceutical management for women undergoing treatment for breast cancer.

Chapter One

1. INTRODUCTION

Cancer (Ca) is a group of diseases characterized by uncontrolled and growth spread of abnormal cells. It may be caused by internal factors (inherited mutation, hormonal, immune, conditions and mutation from metabolism) or external ones (tobacco, radiation, chemicals and infectious organisms) (Kumark and Clark, 2005). Cancer is prevalent all over the world among developed and developing nations; it affects both sexes at all ages. Breast cancer is the first leading cause of death of female cancers. Over 175,000 women in the US are diagnosed with breast cancer each year, the prevalence rising up to 7% over age 70 in the near future (LouWman *et al*., 2007). It occupies the first of female's Ca among the Palestinians with incidence (15.1) per 100,000 population, and mortality rate (5.2) per 100,000 females (MOH report, 2005). Ca treatment is based on chemotherapy, radiotherapy and surgical interventions. Radiotherapy is available at Auqasta vectoria hospital(AVH) at Al-Alquds in the Palestinian territories, but the other two types are accessible at most governmental health settings at Gaza Strip and West Bank (WB).

Chemotherapy is an important treatment in cancer care and is associated with numerous side effects such as bone marrow suppression, increased susceptibility to infection, nephrotoxicity, anorexia, alopecia, cupress, nausea and vomiting (Vincent *et al*., 2001). Early studies reported that patients cited nausea and vomiting as the most distressing symptoms when receiving chemotherapy (Coates *et al*., 1983; Deboer-Dennert *et al*., 1997). Beyond their distressing effects, sever nausea and

vomiting can lead to nutritional deficiencies, dehydration and electrolyte imbalance and fatigue (Hawthorn 1995, Joss *et al*., 1990; king 1997).

Historically, antiemetic treatment has been improved first by the introduction in 1981 of high-dose metoclopramide which reduced the amount of emesis (Gralla *et al*., 1981), second by the development of serotonin (5-HT3) antagonist in the early 1990s, potentiated by concomitant use of corticosteroids which further improved control of emesis (Grunberg & Kesketh, 1993). Despite these improvements, nausea and vomiting remain a problem for patients. Recently a new drug, the neurokinin NK (1) receptor antagonist has been shown to have a better effect on preventing both acute and delayed CINV for patients treated with highly emetogenic chemotherapy (Dando & Perry, 2004; Dewit *et al*., 2004). Non-pharmacological interventions such as music (Ezzone *et al*., 1998), acupressure (Dibbel *et al*., 2000) and progressive muscle relaxation (Molassiotis *et al*., 2002) have also been shown to reduce CINV.

The 5-HT_3 antagonists are more effective than prior medications in preventing chemotherapy induced vomiting (DeMulder. 1990; Marty, 1990; Roscoe *et al*., 2000; Osoba *et al*., 1997). However, chemotherapy related nausea is not as well controlled by these drugs and remains a significant problem (Roscoe *et al*., 2000). Uncontrolled nausea and vomiting (NV) can interfere with adherence to treatment regimens, and may cause oncologists to reduce chemotherapy doses (Morrow and Dobkin 1988; Stewart, 1990). Nausea and vomiting can also disrupt the activities of daily living, cause lost time from work, increase anxiety and depression, (King, 1997).

In one study involving 1,413 cancer patients undergoing chemotherapy, 80% experienced nausea to some degree, with 40% having at least one episode of vomiting (Roscoe *et al*., 2000). Similarly, in a study, 76% of 322 patients who received chemotherapy regimens containing cisplatin, carboplatin, or doxorubicin experienced nausea following their first treatment, despite what was felt by physicians to be adequate antiemetic prophylaxis. Of these 322 patients, 147(46%) had nausea of moderate to severe (Hickok *et al*., 2003). Identifying methods to successfully prevent and alleviate treatment-related nausea remains a major clinical challenge.

Since pharmacological treatments have failed to completely manage NV, exploring the complementary role of other, non-pharmacological, approaches that can be used in addition to pharmacological approaches becomes paramount. Acupressure at the P6 point is a value-added technique in addition to pharmaceutics; management for women undergoing treatment for breast cancer to reduce the amount and intensity of delayed CINV, since up to 60% of patients had been reported nausea despite the use of anti emetics (Dibble *et al*., 2007). Interestingly, several studies reviewed by Morrow and Roscoe (1997) have found that women, compared to men, are more susceptible to nausea caused by classical conditioning, as evidenced by the fact that women are more likely to experience nausea in anticipation of chemotherapy.

Stimulation of the P6 acupuncture point located on the inside of the wrist with needles (acupuncture) or pressure (acupressure) has been used to relieve NV in Traditional Chinese Medicine (TCM) for centuries (Beinfield and Korngold, 1995). Literature reviews indicate that acupuncture and acupressure may provide relief of these symptoms (Kaptchuk, 2002;

Mayer, 2000; Vickers, 1996). Specifically, needling or applying pressure (generally with an acupressure band such as the Sea Band®, (Sea Band UK Ltd., Leicestershire, England) to an acupoint have been efficacious in alleviating morning sickness (Belluomini *et a*l, 1994; Carlsson *et al*., 2000; De Aloysio and Penacchioni, 1992; Norheim *et al*., 2001; Evans *et al*., 1993; Slotnick, 2001), motion sickness (Hu, 1992, 1995; Bertolucci and DiDario, 1995; Stern *et al*., 2001; Alkaissi 2005), post-surgical nausea (Fan et al., 1997; Ferrara-Love *et al*., 1996; Gieron *et al*., 1993; Harmon et al., 2000; Ho *et al*., 1996; Stein *et al*., 1997; Alkaissi 1999, 2002; Zarate *et al*., 2001) and NV associated with chemotherapy (Dundee 1989,1991; Roscoe, 2002, 2003; Shen *et al*., 2000; Dibble, 2000; Williams *et al*.,1992; Treish *et al*., 2002; Bushunow *et al*., 2002; Dundee and Yang; 1990; Stannard, 1989; Pearl *et al*.,1999; Noga *et al*., 2002).

Beginning in the early 1990s, studies assessing the efficacy of electrical stimulation (acustimulation) using portable Transcutaneous Electrical Nerve Stimulator (TENS) Wrist Bands to the P6 acupuncture point for control of nausea have also been conducted. All of these studies used the Relief Band (Woodside Biomedical, Carlsbad, CA), which is marketed for this purpose and has United States Food and Drug Administration (FDA) clearance as treatment for NV. In 1998, the National Institutes of Health Consensus Statement on Acupuncture concluded that promising results have emerged showing the efficacy of acupuncture in adult postoperative and chemotherapy induced nausea and vomiting. The acupuncture point, P6 had been the point used in most of the trials (Ezzo *et al*., 2006).

Acupressure seems to be a good way to complement antiemetic pharmacotherapy, as it is safe, convenient and with minimal costs involved. These make it a cost-effective intervention. It is not known why acupressure works, and partly these results may be attributed to a placebo effect, as also highlighted in the study by (Roscoe *et al*., 2003; Burish *et al*.,1992) declared that psychological reasons may also partly explain these results. Indeed, it was previously reported that relaxation and distraction techniques have significantly improved nausea and vomiting in breast cancer patients receiving chemotherapy (Molassiotis, 2002). Acupressure is easily learnt and taught and patients should be informed about its potential role and taught how to apply it. Self-administered acupressure appears to have a protective effect for acute nausea (Ezzo, 2007).

There have been recent advances in chemotherapy-induced nausea and vomiting using 5-HT_3 inhibitors and dexamethasone. However, many still experience these symptoms, and expert panels encourage additional methods to reduce these symptoms (Ezzo *et al*., 2007). Research supports the effectiveness of acupuncture and acupressure for the treatment of chemotherapy-induced nausea and vomiting. Used in conjunction with current antiemetic drugs, acupuncture and acupressure have been shown to be safe and effective for relief of the nausea and vomiting resulting from chemotherapy (Collins, 2004).

Studies have confirmed that the key to successful management of CINV is to prevent symptoms before they occur (Goodman 1997; Morrow et al 1998). Assessment evaluation of a cancer patient's general condition and a determination of how he or she feels is the first step in managing symptoms (Dodd *et al* 2001). Different approaches to symptom assessment

may be adapted, from unstructured communication between patients and healthcare professionals to the use of documentation such as checklists or diaries. Research suggests that systematic assessment of symptoms is associated with reduced symptom distress over time (Sarna 1998).

Chemotherapy-induced nausea and vomiting is classified as either "acute" within 24 h post chemotherapy or "delayed" nausea that occurs on days 2–5 of the chemotherapy cycle is particularly troublesome because there is no reliable pharmacological treatment for this problem (Morrow *et al*., 1996, 1998). The American Society of Clinical Oncology (ASCO) recommendations include giving potential 5-HT_3 receptor antagonists plus corticosteroids before chemotherapy to patients receiving chemotherapy that are at high risk of emesis. Nevertheless, many patients still experience nausea and vomiting related to chemotherapy. Therefore, the expert panels emphasize the need for evaluation of additional ways to reduce these symptoms (Gralla *et al*., 1981; Hesketh *et al*., 1998). The need for additional relief has led to interest in non-pharmacological adjuncts to drugs like acupuncture or acupressure. Combining anti emetics with other non-pharmacological treatments may prove more effective in decreasing nausea than anti emetics alone (Molassiotis *et al*., 2006).

The first aim of this study is to examine the efficacy of P6-acupressure in preventing chemotherapy induced nausea and emesis associated with highly emetogenic chemotherapy (i.e., doxorubicin as adjuncts to standard 5-HT_3 receptor antagonist antiemetic (granisetron) and dexamethasone in reducing acute nausea (during the day of treatment) and delayed nausea (2-5 days) following the day of chemotherapy).

The second aim is to examine the efficacy of the acupressure bands with stimulation of P6 in reducing vomiting and in maintaining quality of life (QOL).

1.1 BACKGROUND

1.1.1. Mechanisms of Chemotherapy induced vomiting (CIV): Serotonin

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has been shown clinically to be an important mediator of the early ("acute") phase of CIV. Preclinical studies have shown that cisplatin causes a calcium-dependent exocytic release of serotonin from enterochromaffin cells in the gastrointestinal tract, possibly as a result of free radical generation (Andrews, 1998; Matsuki, 1993). The released serotonin then activates receptors on vagal afferent fibres, which stimulates the CNS centres that mediate the emetic response (Andrews, 1998; Matsuki, 1993). These receptors are known to be of the 5-HT_3 subtype, as 5-HT_3 receptor antagonists inhibit the acute emetic response in a ferret CIV model (Costall *et al.*, 1986; Miner & Sanger, 1986), an observation which generated further interest in the role of serotonin.

Cisplatin administration to humans has also shown clear evidence for the involvement of serotonin. After cisplatin administration, there ensues a large increase in the urinary output of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) within 24 h indicating the release of intracellular serotonin (Cubeddu, 1996). The time course of this response in the acute CIV period appears to correlate well with the clinical efficacy profile of 5-HT_3 receptor antagonists, which are most active against the

acute-phase CIV associated with cisplatin-based chemotherapy (Cubeddu, 1996).

Although the predominant therapeutic effect of 5-HT_3 receptor antagonists is believed to be antagonism of peripherally released serotonin, a central effect cannot be completely excluded. 5-HT_3 receptors have been shown to exist in the area postrema NTS, sub nucleus gelatinous and in lower densities in the dorsal motor nucleus of the vagus and the spinal trigeminal tract of a number of species including man (Barnes e*t al.,* 1990; Leslie *et al.,*1990; Palacios et al., 1991; Pratt and Bowery, 1989; Radja *et al*., 1991; Reynolds *et al*.,1991). It has been shown in dogs that antagonism at 5-HT_3 receptors located within the blood–brain barrier can block cisplatin-induced emesis (Gidda,1995), but the relevance of this finding to the path physiology of CIV in humans is unclear, as plasma levels of 5-HIAA are not increased by cisplatin in dogs (Nakajima *et al*., 1996). Higgins and colleagues reported that in the ferret, emesis induced by cisplatin was attenuated, but not blocked, by infusions of 5-HT_3 receptor antagonists into the area of postrema (Higgins *et al*., 1989), although the 5-HT_3 selective agonist 2-methyl 5-HT did not reproducibly induce emesis when infused via the same route. It is therefore unclear whether 5-HT_3 receptor antagonists have any central activity in humans. It is widely assumed that the major antiemetic activity of 5-HT_3 receptor antagonists occurs through inhibition of afferent vagal stimulation in the periphery. Andrews and colleagues have reported that although ferrets are initially refractory to radiation-induced emesis following vagotomy, the emetic reflex returns in some animals (Andrews and Bhandari, 1993). This finding suggests that emetic reflex pathways may have some plasticity, and could help to explain why the antiemetic effects of 5-HT_3 receptor antagonists are

more pronounced in some patients than in others. Although important in the acute phase, serotonin is not believed to be a significant mediator of emesis occurring more than 24 h after chemotherapy (historically known as delayed vomiting). Delayed CIV responds poorly to 5-HT_3 antagonists in both humans and animal models (Cubeddu, 1996), and it is therefore highly likely that other neurotransmitters are involved in the pathogenesis of delayed-phase symptoms.

1.1.2. Mechanisms of CIV: substance P

Substance P, a member of the tachykinin family of neuropeptides, was first implicated as a potential mediator of vomiting when Amin et al., (1954) described high levels of this peptide in the area postrema of dogs. Subsequently, studies in ferrets showed that the potent capsaicin analogue resinferatoxin blocked the emetic response to both centrally and peripherally acting emetic agents (Andrews & Bhandari, 1993). It was suggested that this antiemetic effect was mediated by resinferatoxin-induced depletion of sensory neurotransmitters such as substance P in the NTS in the brainstem. In support of this concept, animal studies using both centrally and peripherally active emetogenic stimuli demonstrated that vomiting was prevented by non-peptide antagonists of the neurokinin-1 (NK_1) receptor, a site at which substance P is thought to act (Diemunsch & Grelot, 2000; Bountra *et al*., 1993; Tattersall *et al*., 2000).

Substance P is co-localised with serotonin in enterochromaffin cells in the gastrointestinal tract, and substance P levels in the peripheral circulation have been reported to be elevated following cisplatin administration in patients (Matsumoto, 1999). Substance P has been shown in animals to cross the blood – brain barrier, which raises the possibility

that substance P of peripheral origin, may act centrally to induce emesis (Freed *et al*., 1996). CNS penetration by the NK_1 receptor antagonists has been shown to be essential for the prevention of vomiting in the first 4 hours following cisplatin-based chemotherapy, which suggests that the antiemetic effect of NK_1 receptor antagonists is mediated centrally, probably in region of the NTS (Tattersall, 1996). The spectrum of antiemetic activity observed with NK_1 receptor antagonists in preclinical studies was broader than with other antiemetic such as 5-HT_3 receptor antagonists. Specifically, NK_1 receptor antagonists prevented both acute and delayed vomiting induced by capsulation in the ferret (Diemunsch, 2000; Tattersall, 2000), whereas 5-HT_3 receptor antagonists prevented only acute vomiting in this model. These preclinical data, especially those derived from the ferret model of CIV, were compelling enough to justify clinical evaluation of NK_1 receptor antagonists.

1.1.3. Chemotherapy

1.1.3.1 Doxorubicin (Adriamycin®) or hydroxyldaunorubicin

It is a DNA –interacting drug widely used in chemotherapy. It is commonly used in the treatment of a wide range of cancers. The drug is administered by injection. It may be sold under the brand names Adriamycin PFS, Adriamycin RDF, or Rubex (Mayo clinic, 2007). The main benefits of this form are a reduction in cardio toxicity

Clinical Use of Doxorubicin

Doxorubicin is commonly used to treat some leukaemia, Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissues sarcoma, multiple, and others (Mayo clinic, 2007).

Commonly used doxorubicin-containing regimens are Ca (cyclophosphamide, Adriamycin), TAC (Taxotere, CA), ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), CHOP (Cychlophosphamide, Adriamycin, Vincristine, Prednisone) and FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide

Side Effects of Doxorubicin

Acute side-effects of doxorubicin can include nausea, vomiting, and heart arrhythmias. It can also cause Neutropena (a decrease in white blood), as well as complete alopecia (hair loss). When the cumulative dose of doxorubicin reaches 550 mg/m², the risks of developing cardiac side effects, including congestive heart failure, dilated cardiomyopathy, and death, dramatically increase (Johansson *et al*., 2006)

4. Acupuncture and acupressure

Acupuncture is a traditional Chinese medicine (TCM) which includes placing physical pressure by the body's surface using fingers to press key points on the surface of the skin to stimulate the body's own healing ability. Once these items are printed by hand, elbow, or by using different devices on different acupuncture points on the body, release the muscle tension and promote blood circulation and vitality of the body's energy to aid healing. According to TCM, there are more than 2,000 acupuncture points connected by 12 major and 8 secondary pathways called meridians (National Center for Complementary and Alternative Medicine ([NCCAM], 2003). These meridians conduct energy, or Qi (pronounced "chee"), throughout the body and are associated with specific organs and organ systems (McCaffrey *et al*., 1997). Spiritual, emotional,

mental and physical health is controlled by the Qi energy, and acupuncture corrects imbalances in Qi energy flow (McCaffrey & Thomas,2003). Acupuncture and acupressure are based on the assumption that an individual's welfare depends on the balance of energy in the body and overall energy level. The hypothesis that energy flows in the body along paths according to the meridians and that it is possible to restore the balance of energy by manipulating these meridians as acupressure and acupuncture (Vincent & Richardsson, 1986).

Asystematic review summarized 33 controlled studies of P6 stimulation for nausea and vomiting by 27 shows the effect of P6 stimulation, using a variety of forms, including acupuncture, electro acupuncture, transcutaneous electrical nerve stimulation, and acupressure (Vickers, 1996). Affected by this review, a National Institutes of Health Consensus Conference on Acupuncture in 1997 concluded that "promising results have emerged showing efficacy of acupuncture in adult postoperative and chemotherapy induced nausea and vomiting" (National Institute of Health, 1998). However, some of the existing studies, methodological limitations and problems with the control group. There were also questions about the optimal mode of P6 stimulation.

Since the early studies by Dundee et al., (1987, 1989) research has been almost consistently shown that adding acupuncture to antiemetic therapy may significantly reduce nausea and vomiting. In a study of breast cancer patients receiving high emetogenic chemotherapy, Shen *et al*., (2000) have shown that vomiting decreased from a median of 15 episodes of antiemetic single group to a median of 5 episodes of anti emetics plus electro acupuncture group (n = 104). But the non-invasive form of

acupuncture, acupressure, have received little attention in oncology. Acupressure involves the pressure instead of needles on the same points used in acupuncture, but it is safer than acupuncture, cheaper, and patients can easily learn to put pressure on their own.

Only a few studies have been published in chemotherapy patients. An electronic search of MEDLINE, CINAHL and Pub Med from 1990 and May 2005 using the keywords “acupressure” and “nausea” or “vomiting” and “chemotherapy” or “cancer” revealed 10 published studies (Dibble, 2000). Seven of these studies showed positive results and two studies are very close to statistical significance. Only one study showed negative results with an acustimulation method. Among the studies that show significant (or two matches) reduction of chemotherapy-related NV was used three attempts nice strip (a small battery-powered TENS device to stimulate the P6 point defeat) with samples from 18 to 50 patients (Pearl, 1999; Roscoe, 2002; Treish *et al*., 2003), used a Sea Band (an elastic wristband with a round plastic button on the P6 pressure point defeat) in small samples (Dundee and Yang, 1990,1991; Wright, 2005) and two used direct pressure on the P6 acupoint (Shin, 2004) or a combination of P6 and ST36 acupoints (Dibble, 2000; Roscoe *et al*., 2003).

Acupuncture involves using needles, heat, manual and electrical stimulation to manipulate the meridians. Small needles inserted at appropriate places and left in place for approximately 15 to 20 min (Milton, 1998). The needles are about the diameter of a hair and can cause temporary discomfort during insertion, but usually the patient is unaware of the needles (NIH 1997). Practitioners use needles of various gauges, depending on the location and strength of stimulation is desired (Tan *et al*.,

1973). Needles can be manipulated in various ways, such as wirling needles, burning some spices at the end of the needles (Moxibustion) or by low electrical stimulation to increase the stimulation of acupuncture points (Lytle 1996). The use of such technology is dependent on operator preference, (Tan *et al*., 1973).

Acupressure is a therapy similar to acupuncture, and achieved at selected acupuncture points on the body are pressed with fingers, hands, palms, elbows and knees to change the internal flow of energy (Cowmeadow, 1992). Pressing the acupuncture points can alter the energy flow through the body and cause symptoms relief (Milton, 1998). Acupressure can be performed by physicians or patients. The word shiatsu, Japanese, literally meaning "finger pressure". Shiatsu is a form of acupressure massage is included (McCaffrey & Thomas, 2003).

The acupuncture / acupressure points that are used to control NV is Nie-Guan point, also called pericardium 6, or P6, inland port, and S136 mean rang the Three Mile Point (Cerrato, 1997). P6-score divided bilaterally on the pericardium meridian, which is on the inside of the forearm, three finger widths proximal to the wrist first wrist crease and between tendons of Flexor carpi radial and Palmaris longus muscles (Dibble *et al*., 2000). The ST36 point lies along the stomach meridian bilaterally, approximately four finger widths distal to the patella and one finger width lateral to the tibia (Dibble *et al*., 2000).

In 1997, after reviewing the available research, the NIH issued a consensus statement that acupuncture is effective for postoperative dental pain and NV caused by anesthesia, chemotherapy or pregnancy. One of the pivotal studies included 140 patients with chemotherapy, 88 postoperative

patients and 219 pregnant women were randomized to either a group receiving acupuncture or a group receiving conventional treatment. The acupuncture group had significantly reduced symptoms compared with conventional treatment group (Riet *et al*., 1990). Other studies showed that acupuncture can relieve menstrual pain, dental pain, fibromyalgia pain, and tendinitis (Pomeranz, 1996; Portnoy, 1993). There have been conflicting results in studies using acupuncture for the treatment of asthma (NIH 1997). NIH reported on many studies that show that acupuncture has been variable to relieve low back pain including migraine headaches, menstrual cramps, carpal tunnel syndrome, and muscle pain in fibromyalgia and other conditions with chronic pain (NIH, 1997). Discomfort with acupressure bands such as skin irritation, transient pain and swelling in the wrist have been described in a few studies of NV (Lee & Done, 2004;Ezzo *et al*., 2005; Alkaissi, 2002).

Pooled results from eleven randomized controlled trials evaluating acupuncture-point stimulation plus anti emetics for chemotherapy-induced nausea and vomiting showed a significant decrease in the proportion of patients experiencing acute vomiting and a trend toward significance for reducing acute nausea severity (Mezzo *et al*., 2005).

1.1.4.1 Acupressure Mechanism

Several mechanisms of action have been proposed for the effect of P6 on NV. One proposed mechanism is that P6 works through neurotransmitters. Many experimental studies have shown that acupuncture influences the endogenous opioid system (Han & Terenius, 1982), as well as, serotonin transmission via activation of serotonergic and noradrenergic fibers (Mao *et al*., 1980). These chemicals either change uncomfortable

experience (e.g., pain, nausea, and vomiting) or release other chemicals that influence the body's self-regulating system, including the immune system (NIH, 1997). A neural mechanism has been suggested based on the ability of local anaesthetic to block the antiemetic action of P6-acupressure (Dundee & Ghaly, 1989). Both manual acupuncture and electro-acupuncture analgesia may be blocked by the opioid antagonist naloxone (Pomeranz and Chiu, 1976). Clement-Jones et al., (1980) reported that B-endorphin-like immunoreactivity in cerebro spinal fluids(CSF) increased during low-frequency electro-acupuncture, whereas met-encephalin concentrations did not change. In contrast, met-encephalin levels but not B-endorphin, increased in CSF after high-frequency electro-acupressure (Clement-Jones *et al*., 1979).

The biochemical changes, although not completely understood, may stimulate the body's natural healing abilities and promote physical and emotional well-being. Becker, (1970) using galvanic-skin response measurements, demonstrated that electrical currents flowed along traditional acupuncture meridians. He showed that 25% of acupuncture points existed along these meridians and could stimulate electrical conductivity where no other explanation could be found for changes in the electrical conductivity (Becker, 1970).

A second proposed P6 mechanism is through direct influence on the smooth muscle of the gut. Electro stimulation of P6 has reduced gastric tachyarrhythmia in induced motion sickness studies (Hu *et al*., 1995; Stern *et al*., 2001) and enhanced the percentage of regular slow waves seen by electrogastrography. Electro acupuncture at P6 has decreased period-dominant frequency in the electro astrograph. Electro acupuncture at P6

suppressed retrograde peristaltic contractions and reduced vomiting episodes in seven conscious dogs with vasopressin-induced emesis (Tatewaki *et al*., 2005). This effect was abolished by naloxone, so the authors concluded that a central opioid pathway was involved.

A third proposed mechanism is that P6 works through a somato visceral reflex. Electro stimulation at P6 has inhibited the rate of transient lower oesophageal sphincter relaxations triggered by gastric distension in healthy volunteers while sham acupuncture did not (Zou *et al*., 2005). In contrast to the previous study (Tatewaki *et al*., 2005), this effect was not inhibited by naloxone, thus, suggesting a non-opioid mechanism. Zou et al., (2005) speculated that a somatovisceral reflex, which has been previously demonstrated to affect gastric motility in rats (Sato *et al*., 1993), could be involved.

A fourth proposed mechanism is that P6 works through sensory input inhibition. According to this theory, when sensory input from gastric distension is inhibited, it leads to an inhibition of the frequency of transient lower oesophageal sphincter relaxations. Because acupuncture had no influence on the residual lower oesophageal sphincter pressure or on the duration of lower oesophageal sphincter relaxations, it seems unlikely that acupuncture acts primarily on the efferent motor pathway (Zou *et al*., 2005).

A fifth mechanism suggests P6 stimulates a somatosympathetic reflex that induces gastric relaxation. The reflex centre is within the medulla, and the ventrolateral medulla neurons may play an important role (Tada *et al*., 2003).

A sixth proposed mechanism is that P6 can increase vagal modulation. Huang et al., (2005) proposed that vagal modulation could be examined through heart rate variability analysis. Normalized high-frequency power was used as the measure of vagal modulation. Normalized high-frequency power increased in the P6 group but not the sham acupuncture or no-treatment groups, thus, suggesting vagal modulation through P6 (Huang *et al*., 2005).

A seventh proposed mechanism is that P6 may influence the cerebella vestibular neuro matrix. In a functional magnetic resonance imaging study, acupuncture at P6 selectively activated the left superior frontal gyres, anterior cingulated gyres, and dorsomedial nucleus of thalamus whereas sham acupuncture or tactile stimulation did not (Yoo *et al*., 2004). P6 acupuncture also selectively activated several structures in the cerebellum suggesting that P6 for motion sickness may work through the cerebella vestibular system.

1.1.4.2. Psychological aspects of acupuncture and NV

The impact of psychological factors on NV is widely acknowledged, and the efficacy of influencing these psychosomatic aspects, e.g. by behavioural therapy or hypnosis, has been demonstrated (Mundy *et al*., 2003). Thus, a psychological effect of acupuncture treatment has been hypothesized. Acupuncture appears to be effective for depression (Allen *et al*., 1998) and for psychosomatic disorders of the gastrointestinal tract (Rohrbock *et al*., 2004; Schneider *et al*., 2005). In the case of depression, these effects could be derived by the influence of acupuncture on the autonomous nervous system (Chambers & Allen, 2002). However, significant placebo effects also must be addressed, as was shown recently

for irritable bowel syndrome (Schneider *et al*., 2005). Determinants of placebo response could be high disease coping capacities (Schneider et al., 2005a), expectations (Vase *et al*., 2003), and suggestibility (De Pascalis *et al*., 2002). Additionally, the treatment response seems also to be related to cognitive aspects (Kreitler *et al*., 1987) and perception of bodily sensations during the acupuncture treatment (Schneider *et al*., 2005b).

1.1.4.3. Stimulation

Acupuncture points can be stimulated by various methods, including invasive and non-invasive stimulation. The Sea Band ® (Sea-Band Ltd., Leicestershire, England) is one of the most common forms of P6 stimulation because it is noninvasive and easy to apply. The band includes a plastic button or beads that can be placed on the P6 to apply pressure, which is then defined as acupressure. Acupressure can also be used by pressing acupuncture points with one´s fingers. In recent studies, Relief-Band ® (Woodside Biomedical Inc., Abbott Park, IL, Maven Laboratories, and Citrus Heights, CA) was used. It is a wristwatch and includes a device that applies surface electrical current at acupuncture point. Transcutaneous electrical stimulation is also used.

1.1.5. Anti emetics

Nausea and vomiting are two of the most distressing side effects of chemotherapy. A variety of antiemetic agents are available, including antihistamines, dopamine-receptor antagonists, serotonin-receptor antagonists, and neurokinin-receptor antagonists. To ensure optimal symptom control for each patient without unnecessarily prolonging treatment, patient- and treatment-specific risk factors must be considered.

Neurokinin-receptor antagonists, the newest class of antiemetic, are effective in preventing acute and delayed CINV but must be used in combination with a serotonin-receptor antagonist and a corticosteroid. Guidelines recommend the use of 5-HT3 receptor antagonists as a pharmacologic intervention for acute and delayed nausea and vomiting for moderately and highly mutagenic chemotherapy. Although newer anti emetics and 5-HT3 receptor antagonists are available, ondansetron and granisetron are still used widely. The results of a review of the literature study reveal that ondansetron and granisetron have equal antiemetic efficacy in reducing or eliminating (CINV), with the evidence classified as good for judging the strength of the overall evidence. Although side effects of ondansetron and granisetron have been reported, they normally are mild and of brief duration, not severe or lasting enough to warrant discontinuation (Vrabel, 2003).

It is well known that dexamethasone is highly effective in managing delayed nausea and vomiting (Roila, 2006), although many clinicians are sceptical of the use of steroids for prolonged periods of time. Hence, the use of dexamethasone may have contributed to the better control of NV in the study by Roscoe *et al*., (2003).

1.1.5.1. 5-HT3 receptor antagonists

Ondansetron, granisetron, tropisetron, dolasetron and ramosetron

Members of this group exert their effect by binding to the serotonin 5-HT3 receptor in the CTZ and at vagal afferents in the gastrointestinal tract. They have been used as prophylaxis and treatment of NV due to chemotherapy and radiation therapy (Dicato and Freeman, 1992) and

PONV (Lee *et al*., 2002). There is no evidence of any difference in the efficacy and safety profiles of 5-HT3 receptor antagonists in the prophylaxis of PONV (Gan *et al*., 2003). These drugs are most effective when given at the end of surgery (Henzi, 2000).

Granisetron is a selective antagonist of 5-HT3 receptors and is thought to elicit its antiemetic effect by blocking 5-HT3 receptors at both peripheral and central sites (Sanger *et al*., 1989). The onset of the antiemetic action of granisetron occurs within approximately 30 minutes after a single intravenous administration, with a duration of action of more than 24 h (Furue *et al*., 1990). Granisetron is reportedly more potent and has a longer lasting therapeutic effect than ondansetron (Andrews, 1992). These findings may be due to the higher specificity and affinity of granisetron for 5-HT3 receptors (Andrews, 1992).

1.1.5.2. Dexamethasone

Dexamethasone has mainly glucocorticoid mechanism of action and effect, which means that the preparation has anti-inflammatory effects (Splinter *et al*., 1997, 1998). Dexamethaone acts by inhibition of prostaglandin synthesis and / or serotonin turnover in the CNS and intestine (Fredrickson, 1992; Aapro 1984) and by the release of endorphin (Harris *et al*., 1982). Glucocorticoid receptors in the nucleus tractus solitaries nucleus of raph and area postrema in the brainstem play a major role in the transfer of impulses to the vomiting centre (Watcha, 1992). Dexamethasone has some antiemetic effect on chemotherapy-induced nausea (Henzi, 2000).

Chapter Two

2. LITTERATURE REVIEW

2.1 Studies with Positive Findings

Numerous studies have tested the effectiveness of acupuncture, acupressure and acupressure and acupuncture used together for alleviating CINV. Few have focused on acupuncture alone.

A study that focused on acupuncture alone was a study by Shen and colleagues, (2000). This was a three-arm, parallel-group, randomized controlled trial with a 5-day study period. All the patients (n=104) were receiving the same antiemetic pharmacotherapy and high-dose chemotherapy and were randomly assigned to different groups. The first group (n= 37) received low- frequency electro acupuncture at P6 and ST36 points. The second group (n= 33) received minimal needling at P6 and ST36 but had mock electro stimulation, and the control group (n= 34) received no acupuncture. The results indicated that the group receiving electro acupuncture had significantly fewer episodes of nausea ($p < 0.001$) compared to the other groups. Those receiving minimal needling had fewer episodes of emesis than did the control group ($p = 0.01$) (Shen *et al*., 2000).

There has been one study evaluating the combined use of acupressure and acupuncture in reducing chemotherapy-induced nausea and vomiting. In an uncontrolled study (n= 40) by Dundee and Yang (1990), the researchers found that use of an elasticized wrist band with a stud placed over the P6 acupuncture point (Sea Band) pressed every 2 hr prolonged the antiemetic effect of the acupuncture for up to 24 hr. This study followed two groups of patients: one group that was hospitalized (n=

20) and one group of outpatients (n= 20). In the hospitalized group, 100% reported improvement in symptoms, but in the outpatient group, only 75% reported improvement (Dundee & Yang, 1990).

A study by Dibble and colleagues (2000) compared the differences in patients receiving the usual allopathic antiemetic treatment to those receiving allopathic treatment plus acupressure. The study, conduct at an outpatient oncology clinic in a major teaching medical centre and at a private outpatient oncology practice, involved 17 women undergoing adjuvant chemotherapy for breast cancer for a single chemotherapy cycle (21 to 28 days) (Dibble *et al*., 2000). The women were randomized into two groups, with the control group (n= 9) receiving the allopathic antiemetic therapy only. Women in the treatment (acupressure) group (n= 8), in addition to receiving allopathic antiemetic therapy, were taught how to access the P6 and ST36 acupressure points and were told to hold steady pressure on the points for a maximum of 3 min every morning and as needed for symptom relief. Researchers noted statistically significant difference related to the nausea experienced ($p < 0.01$) and the nausea intensity ($p < 0.04$) compared with the women in the acupressure group and those in the control group (Dibble *et al*., 2000).

Roscoe (2000) provided support for the use of acupressure bands as an adjunct to pharmacological anti emetics for control of chemotherapy related nausea. Patients randomized to the acupressure band condition had significantly less nausea on the day of treatment than patients in the control condition. This reduction in nausea did not extend to the delayed phase following treatment (Days 2–5), nor was there a reduction in emesis. It cannot be ascertained from data why the bands were helpful on the day of

treatment but not on the following days. It may be related to the fact that the acute and delayed treatment-related nausea have different etiologist, as evidenced by the fact that the 5-HT_3 class of anti emetics are more effective than the old line anti emetics for control of acute nausea but are less effective than the older drugs for control of delayed nausea (Roscoe, 2000).

A study of 160 breast cancer women who were beginning their second or third cycle of chemotherapy treatment and had moderate nausea intensity scores with their previous cycles, the participants were randomized to one of three groups: acupressure to P6 point (active), acupressure to SI3 point (placebo), or usual care only. All subjects completed a daily log for 21 days containing measures of NV and recording methods (including anti emetics and acupressure) used to control these symptoms. The author concluded that acupressure at the P6 point is a value-added technique in addition to pharmaceutical management for women undergoing treatment for breast cancer to reduce the amount and intensity of delayed CINV (Dibble, 2007).

In a study, examined the efficacy of acupressure wristbands, compared with standard care alone and acustimulation wristbands, in preventing severe nausea among 86 breast cancer patients receiving doxorubicin-based chemotherapy who were at high risk of experiencing severe nausea following treatment. Significant differences in the proportion of patients who reported severe nausea were observed across three conditions (standard care, standard care with acupressure bands, and standard care with an acustimulation band). The proportion of patients in the acupressure band group who reported severe nausea following their chemotherapy treatment (41%) was significantly less than that of the

standard care group (68%) and the acustimulation band group (73%). These findings showed that acupressure wristbands were efficacious and may be an appropriate form of adjuvant therapy for nausea management for breast cancer patients, especially those who are most at risk for experiencing severe nausea following chemotherapy treatment (Roscoe *et al*., 2006).

Treish and colleagues (2003) conducted a randomized study in which 50 patients wore either active or placebo acustimulation bands for five days after chemotherapy as an adjunct to standard antiemetic medications. Those wearing the active band reported significantly less nausea and significantly fewer episodes of vomiting compared to patients wearing the placebo bands. Pearl and colleagues (1999) examined the efficacy of acustimulation in 42 patients in a randomized, double-blind, placebo-controlled crossover trial, with a follow-up. For the 18 patients who completed the crossover component of the study, patients in the active band cycle, as compared to the placebo band cycle, reported a significantly lower severity of nausea during the second through fourth post-treatment days.

In a large multi-Centre study that directly compared the effectiveness of acustimulation bands versus acupressure bands (Sea Band), as an adjunct to 5-HT_3 receptor antagonist antiemetic given as part of routine care (Roscoe *et al*., 2003). A total of 739 (male = 57) patients scheduled to begin their first treatment with either cisplatin or doxorubicin were randomly assigned to wear bilateral Sea Bands, one Relief band, or no band. Pronounced gender differences in efficacy were found. Fewer men vomited in the Relief band (16%) compared to the no band (50%) condition ($P = 0.03$). Men who wore the Relief band also experienced less nausea on

the day of treatment ($P < 0.05$) and less nausea overall ($P < 0.05$). There were no significant differences in any outcome measures between the acustimulation and the acupressure treatment conditions. By contrast, acustimulation band was not helpful for women. The reduction in nausea on the day of treatment in the acupressure band compared to the no band condition, however, closely approached statistical significance ($P = 0.052$) (Roscoe *et al* 2003).

Interestingly, when expected efficacy of the wrist bands was considered, differences in the severity of nausea by whether or not patients thought the bands would be effective were observed in those patients assigned to the acupressure condition, but not for those in the a custimulation condition. Patients who received the acupressure bands and expected them to be effective ($n = 112$) experienced less nausea on the day of treatment and also less overall nausea compared those who did not expect them to be effective ($n = 121$) and to the no band control group ($n = 233$) ($P < 0.05$) (Roscoe *et al*., 2003).

In a randomised controlled trial, acupressure were applied using wristbands (Sea Band™) in which patients in the experimental group had to wear it for the 5 days following the chemotherapy administration. Assessments of nausea, retching and vomiting were obtained from all patients daily for 5 days. Thirty-six patients completed the study from two centres in the UK, with 19 patients allocated to the control arm and 17 to the experimental arm. It was found that nausea and retching experience, and nausea, vomiting and retching occurrence and distress were all significantly lower in the experimental group compared to the control group ($P < 0.05$). So Results highlight the important role of safe and

convenient non-pharmacological complementary therapies, such as acupressure, in the management of the complex symptoms of chemotherapy-related nausea and vomiting (Molassiotis *et al*., 2006).

2.2 Studies with Negative Findings

In a study of Roscoe (2005) examined the efficacy of an acustimulation wrist band for the relief of chemotherapy-induced nausea using a randomized three-arm clinical trial (active acustimulation, sham acustimulation, and no acustimulation) in 96 women with breast cancer who experienced nausea at their first chemotherapy treatment. There were no significant differences in any of these study measures among the three treatment conditions ($P > 0.1$). Study results do not support the hypothesis that acustimulation bands are efficacious as an adjunct to pharmacological antiemetic for control of chemotherapy-related nausea in female breast cancer patients (Roscoe *et al*., 2005).

2.3 Statement of the problem

Complete control of CINV remains elusive despite decades of research on pharmacological anti emetics. Nausea, in particular, remains a significant problem with as many as 75% of patients reporting the symptom at some point following their treatment. Approximately one-third of patients have nausea of at least moderate intensity resulting in a significant reduction in quality of life(QOL). Delayed nausea that occurs on days 2–5 of the chemotherapy cycle is particularly troublesome because there is no reliable pharmacological treatment for this problem. Not surprisingly, considerable effort and interest continue to be focused on developing better control of NV. Our difficulty in completely managing chemotherapy-

related NV may stem from the multiple pathways involved in the development of nausea and vomiting including the chemoreceptor trigger zone in the brain, dopamine receptors, personality, vestibular dysfunction, age, anxiety and psychological mechanisms. Despite advances in antiemetic research over the past decade and the introduction of 5-hydroxytryptamine 3 (5-HT3) and Neurokinin1-receptor (NK1) antagonists, chemotherapy-related NV remain a significant problems for the patients, decreasing their QOL and negatively affecting their treatment experience, and impacting physical, cognitive, social, emotional and role functioning.

2.4 The Importance of the study

Early studies reported that patients cited NV as the most distressing symptoms when receiving chemotherapy. Beyond their distressing effects, severe NV can lead to nutritional deficiencies, dehydration, electrolyte imbalance and fatigue. Despite continuing improvements in antiemetic therapies, NV following chemotherapy treatment for Ca remains a significant clinical problem for many patients. Acupressure is a non-invasive, simple method that can be used with good results, no side effect or discomfort, and less cost in relieving NV among breast cancer patients receiving chemotherapy drugs. The measurement of patient perspective has become an important component of treatment evaluation in many areas of medicine. There is evidence that the patients´ view differs from their clinician's judgment. Thus there is a need to expand the outcome measures used. Using a questionnaire, which was deemed adequate by the patients, gave a high response rate and showed a wide range of symptoms associated with chemotherapy management. Despite continuing improvements in

antiemetic therapies, NV following chemotherapy treatment for Ca remains a significant clinical problem for many patients. Since pharmacological treatments have failed to completely manage NV, exploring the complementary role of other, non-pharmacological, approaches that can be used in addition to pharmacological approaches becomes paramount. Evidence is emerging that the stimulation of acupuncture points, particularly the Neiguan (P6) acupuncture point is helpful in controlling NV. While no theory that is generally accepted by the scientific community adequately explains how stimulation of the P6 acupuncture point reduces nausea, recent reviews have concluded that the practice does provide relief for a significant proportion of patients.

2.5 Hypothesis

Breast cancer patients undergoing their second cycle of chemotherapy using acupressure wristbands in addition to antiemetics over 5 days will have significantly lower nausea, retching and vomiting compared to breast cancer patients receiving antiemetic only.

2.6 Objectives

The main objective of the current study was to assess the effectiveness of acupressure Wrist Bands in decreasing NV in a homogeneous group of breast cancer patients receiving chemotherapy.

2.6.1. The primary objective is to examine the efficacy of P6-acupressure in preventing chemotherapy induced nausea and emesis associated with highly emetogenic chemotherapy (i.e., doxorubicin as adjuncts to standard 5-HT_3 receptor antagonist antiemetic (granisetron) and dexamethasone as antiemetic given as part of routine care in reducing acute nausea (during

the day of treatment) and delayed nausea (2-5 days) following the day of chemotherapy.

2.6.2. The secondary objectives are to examine the efficacy of the acupressure bands with stimulation of P6 in reducing vomiting and in maintaining Quality of Life (QOL).

2.7 Study Out comes

Five outcomes related to wrist band efficacy are examined. They are: 1) vomiting, 2) incidence & severity of nausea on the day of treatment (acute nausea), 3) incidence & severity of nausea during treatment Days 2–5 (delayed nausea), 4) QOL, and 5) antiemetic medication taken at home.

Chapter Three

3. MATERIAL AND METHODS

The study was approved by the Ethics Committee at the Faculty of Higher Education at An-Najah National University and the Ministry of Health, Nablus Palestine.

Participants

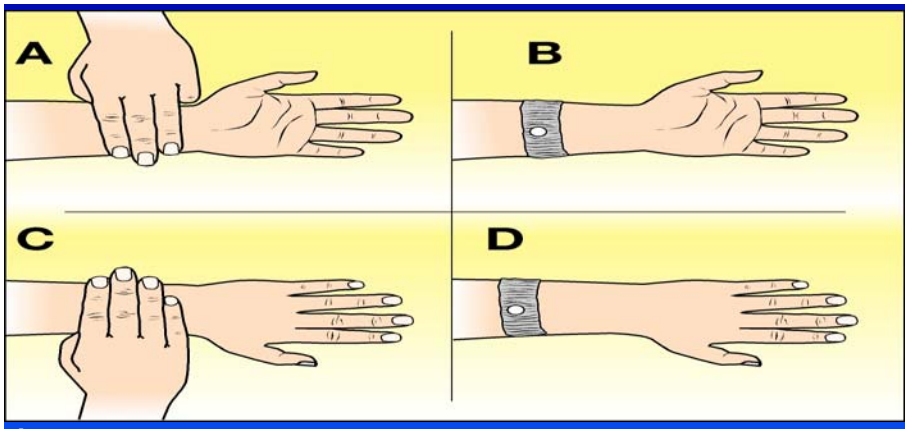
One hundred twenty six women, 18 years of age or older who are beginning their second cycle of chemotherapy for breast cancer treatment and nausea/vomiting with their previous cycle are randomized prior to chemotherapy to one of three groups after obtaining the verbal informed consent, and complete explanation about the study and its importance by the researcher.

Group 1, Acupressure to P6 point (active) (n=42) (Figure 1). The P6 (Neiguan), a point located on the pericardial meridian, which is found three fingers' breadth (approximately 5 cm) proximal to the proximal flexor palmer crease, about 1 cm deep between the tendons of flexor Carpi radials and palmers long us (Figure 1), is supposed to have an effect on nausea and vomiting (A barefoot doctor's manual, 1990). A Sea-Band (Sea- Band UK Ltd., Leicestershire, England) carries a plastic pearl which is fastened to apply pressure on P6. Both forearms are used. These points are marked with water-resistant ink so that the bands could be properly replaced if removed. The areas are draped with a dressing during the stay in the hospital. The nurses giving chemotherapy and the nurses on the ward, although aware that stimulation is being performed, are not aware of the location of P6.

Group 2, Acupressure to none acupoint (placebo) (n=42). A point on the dorsal side of both forearms, four fingers' breadth proximal to the proximal flexor palmer crease was used for placebo stimulation (figure1). These points were marked in the same way as with the active acupressure. Sea-Band was used for stimulation, and the same precautions were taken to keep the stimulation blinded.

Group 3, Usual care only (control) (n=42). These patients were informed in the same way as the acupressure and placebo groups. Instructions for care and assessment are the same, as are the registrations of nausea and vomiting at home.

All subjects complete a daily log for 5 days containing measures of NV and recording methods (including antiemetic) used to control these symptoms.



A *The location of pericardium P6 point (Neiguan):* Is three fingers breadth (patient´s fingers) about 5 cm proximal to the proximal flexor palmar crease, about 1 cm deep between the tendons of flexor carpi radialis and palmaris longus .

B *Active acupressure*: An elastic wristband with a pressure stud, a small button the size of a pea (7mm) *Seaband* (SeaBand®, UK Ltd., Leicestershire, England) was placed bilaterally before anaesthesia over the P6 point.

C *The location of a non-acupoint*. A point on the dorsal side of the forearms, four fingers breadth (patient`s fingers) proximal to the flexor palmar crease was used for stimulation.

D *Pressure on a non-acupoint: Seabands* were placed bilaterally before anaesthesia over *the non-acupoints described under C.*

Figure(1) The location of pericardiumP6 point(Neigumn)and position of acupressure Band in both Active (acupressure) and a non acopoint (placebo) groups. Alkaissi et al 2002

3.1. Design

This is a multicenter, prospective, randomized, consecutive, double-blind and placebo-controlled clinical trial.

3.2. Inclusion criteria

Women with the following criteria were included:

(i) A breast cancer diagnosis, stage of ca I–III, (ii) beginning their second cycle of chemotherapy for breast ca treatment, (iii) had nausea/vomiting with their previous cycle, (iiii) willing to sign a consent form.

3.3 Exclusion criteria

Women were excluded if:

(i) received palliative chemotherapy, (ii) had life expectancy of less than 3 months, (iii) had metastasis disease, (iiii) suffered from bowel obstruction, (v) undergoing concurrent radiotherapy or interferon treatment.

3.4. Informed consent obtained from each subject.

3.5. Period of the study From March 2008 to May 2009.

3.6. Randomization

After agreeing to participate in the study, the patients were randomized using the envelope method. Accordingly, a pack of sealed envelopes including a card with either the word ‘acupressure group’, “placebo group” or ‘control group’ written on it, was given to a staff nurse unrelated to the study; the patient will pick one envelope after she agrees

verbally to take part in the study. Depending on which card was selected patients allocated to their respective group.

3.7. Blindness

The Sea-Bands wrapped with a dressing bandage during the trial period. Neither the observer nor the subjects know if P6 or placebo stimulation was given.

3.8. Prophylactic antiemetic treatment

All patients received standard antiemetic before chemotherapy with a 5-HT_3 receptor antagonist (granisetron 3mg) and dexamethasone 4mg.

Group 1 received granisetron 3mg and dexamethasone 4mg, plus Acupressure to P6 point.

Group 2 received granisetron 3mg and dexamethasone 4mg, plus Acupressure to none acupoint (placebo).

Group 3 received granisetron 3mg and dexamethasone 4mg, and usual care only (a control event group).

The drugs were administered intravenously over 2—5 min immediately before the beginning of chemotherapy.

3.9. Settings

Patients are recruited from three oncology centres located throughout the West Bank (Al Watani Hospital in Nablus, Jeneen & Biet Jala Hospitals).

3.10. Intervention

Acupressure Wrist Bands (Sea-Band™, Sea-Band Ltd., and Leicestershire, UK) were used. These bands are elastic Wrist Bands with a 1cm protruding round plastic button (stud). Patients wear the Wrist Bands with the stud pressing the P6 acupoint, which is located on the anterior surface of the forearm, approximately three-finger width up from the crease of the wrist between the tendons of the Palmaris longus and flexor Carpi radials. Wristbands are used bilaterally.

3.11. Measures

At the time of consent, patients provided demographic information about the patient´s age, marital status and education, details concerning prior experience with NV, for example, nausea during pregnancy, susceptibility to motion sickness, and so on, menstruation, and smoking. Clinical data included the chemotherapy regime and antiemetic used. The patients were asked to assess their degree of nausea during administration of chemotherapy in the hospital. Nausea and vomiting were measured by a patient report diary developed for this purpose by (Burish *et al*., 1987; Carey and Burish, 1988). Each day was divided into 4 segments (morning, afternoon, evening, and night) and patients reported the severity of nausea and number of vomiting episodes for each period on the day of treatment and on the four following days (20 total reporting times). Severity of nausea was assessed on a 7-point rating scale, anchored at one end by 0 = "Not at all nauseated" and at the other end by 6 = "Extremely nauseated." The description "Moderately nauseated" was centred on the scale above the 3. Patients were given the questionnaires to complete at home over the five days immediately following treatment and returned

them to the practice site. Antiemetic rescue medication was used and the number of vomiting episodes was recorded for the same time intervals as part of the diary. Retching counted as vomiting in the antiemetic studies.

3.12. Quality of life(QOL) instrument: FACT-G (Appendix 1)

QOL was assessed using the Functional Assessment of Cancer Therapy Scale-General (FACT-G). The FACT-G is a 27-item scale (higher scores = better QOL developed specifically for use in cancer clinical trials (Cella, 1993). The FACT-G consists of 5 subscales; physical well being (PWB; 7 items), social/family well being (SWB; 7 items), emotional well being (EWB; 6 items), functional well being (FWB; 7 items).It is used internationally and has undergone extensive psychometric testing: test/retest reliability coefficients range from 0.82 to 0.92, internal consistency of subscales measures range from 0.60 to 0.89) (Ward, 1999). The FACT-G is designed for self-assessment to be rated on a 4-point Likert scale. Patients can complete the FACT-G within about 10 min. Each of the inventory questions is scored from 0 (worst possible QOL) to 4 (best possible QOL) with some items being reversed. In addition to an overall quality of life score (the sum of all items), there are subscales for the areas of physical well-being, social well-being, emotional well-being and functional well-being). Patients completed the measure four days after the day of chemotherapy and assessed QOL retrospectively since the treatment (Winstead-Fry and Schultz, 1997).

The sub scores of the FACT-G were calculated according to the directions provided in the FACIT-Manual (all subscales are scored in such a way that higher values mean higher QOL (Cella, 1993).

3.13. A feedback questionnaires were completed by patients at the conclusion of the study period concerning use of diary book, Quality of life instrument: FACT-G (Appendix A), satisfaction and recommendations for the bands. Participants were given questionnaires to complete at home, with instructions to return them back. The study concluded with the return of data following the next chemotherapy treatment.

3.14. Assessment of patient satisfaction

Patients estimated their satisfaction with their NV treatment using a Lickert-type scale 0-6,in which 0 = very much dissatisfied, and 6 = very much satisfied.

Overall patient satisfaction with the band and recommendation of using the Sea Bands as assessed by the feedback question asking whether the patients would recommend that other patients wear a band when receiving chemotherapy.

3.15. Procedures

The study was approved by the Ethics Committee at the Faculty of Higher Education at An-Najah National University and the Ministry of Health, Nablus, Palestine. Informed consent obtained from each subject. The study was double blind and the patients were randomised after accepting entry into the study. One group receives active treatment (n=42), one placebo treatment (n=42) and one group was used as a control (n=42) (Tonato *et al*., 1991; Stubhaug & Breivik, 1995).

Anurse positioned the Sea bands (Sea Band®, UK Ltd., and Leicestershire, England) on both wrists at either the P6 point or on a non-

acupoint just before the start of the chemotherapy (Figure 1). The wrists were wrapped for blinding. The patients were asked to wear the bands continuously for 5 days. If the bands caused discomfort, they could be removed for 30 min every two hours. All patients received a 5-HT_3 receptor antagonist antiemetic (granisetron 3mg) and Dexamethazone 4 mg on the day of treatment before administration of chemotherapy. Antiemetic medications taken during treatment days 2–5 were not regulated but were recorded in a patient diary.

Nausea and emesis were measured by a patient report diary, based on one developed by Burish 1987 and Carey, 1988 that would be completed by patients over a five-day period.

A research coordinator at the study site trained patients in the proper use and placement of the wristband. The placebo points were marked in the same way as for P6 acupressure. The control group followed the same protocol as the P6 acupressure and the non-acupressure groups, but had no Wrist Band and thus was not blinded. Participants were later given the questionnaires to complete at home, with instructions to return them back at the next chemotherapy treatment. Following this, the patients in the P-6 acupressure group and placebo group carried a set of acupressure wrist bands and were instructed to wear them bilaterally throughout the following 5 days taking them off only when they were having a shower or a bath and when the patients were going to sleep. Separate analyses were planned to examine the efficacy of the Wrist Band(s) in controlling acute nausea (occurring on the day of treatment) and delayed nausea (occurring during Days 2–5) because these were clinically relevant distinctions in the treatment of chemotherapy-related nausea. All patients completed the day-

log after the chemotherapy administration and for five consecutive evenings.

3.16 Statistics and analysis

Based on the effect size observed in previous studies, 42 patients are required to achieve a power of 80% at an alpha value set at 0.05 (Cohen, 1992).

Data was coded and entered into SPSS for statistical analysis. Descriptive statistics calculated with all socio demographic and clinical data.

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

3.17 Ethical consideration

The study presented in this thesis is performed in accordance with the Declaration of Helsinki and was approved by the Research Ethics

Committee of the Faculty of Graduate students, An-Najah National University, and Ministry of Health Nablus, Palestine.

Chapter Four

Results and Analysis

One hundred and twenty sex patients were included in the primary data analysis.

4.1 Demographic data and risk factors for nausea and vomiting:

Table (4.1): Demographic characteristics of patients in treatment groups.

	Acupressure n=42	Placebo n=42	Control n=42
Age (ys)	51(13)	53(12)	54(13)
Marital status			
Unmarried n (%)	4(10)	6(14)	5(12)
Married	29(69)	27(64)	27(64)
Widow	8(19)	7(17)	10(24)
Divorced	1(2)	2(5)	
Children (n %)			
Yes	33(79)	30(71)	32(76)
No	9(21)	12(29)	10(24)
No. of children n (%)			
1-6	31(74)	31(74)	24(57)
7-12	11(26)	11(26)	18(43)
Accommodation (%)			
Alone	5(12)	4(10)	7(17)
With spouse	26(62)	22(52)	24(57)
With original family	8(19)	13(31)	8(19)
Others	3(7)	3(7)	3(7)
Education			
Primary	20(47)	18(43)	19(45)
Secondary	12(28)	8(19)	9(22)
Bachelor	4(9)	4 (10)	5(12)
Higher education	6(14)	10(24)	3(7)
Another	1(2)	2(4)	6(14)
Occupation			
Full time	2(5)	4(10)	3(7)
Partial time	3(7)	3(7)	2(5)
House wife	36(85)	34(81)	37(88)
Student	1(2)	1(2)	0(0)

The three groups were similar with respect to demographic characteristics, no statistically significant difference were seen between the groups, homogenisity of a group subjects has implicated for study design. (Table 4.1).

Table (4.2): Risk factors for nausea and vomiting in the acupressure, placebo and control groups.

Variable	Acupressure (n=42)	Placebo (n=42)	Control (n=42)
Health			
Chronic illness	33.3%	28.6%	28.6
No chronic illness	66%	71.4%	71.4%
Nausea in pregnancy	40.5%	33.3%	57.1%
Vomiting in pregnancy	40.5	33.3%	42.9%
Nausea in menstruation	21.4%	33.3%	9.5%
Menstruation vomiting	7.1%	2.4%	7.1%
Motion sickness	21.4%	28.6%	31.0%
Motion vomiting	21.4%	14.3%	21.4%
Smoking	2.4%	0	0

The above table clarifies percentage of risk factors for the participant among the three groups, as we see no differences among the three groups in relation to the above risk factors.

Acute nausea and vomiting/retching:

Table (4.3): Incidence & severity of nausea, vomiting/retching of patients in the treatment groups during first 24 h following chemotherapy.

Day one, during first 24 h following chemotherapy	Acupressure (n=42)	Placebo (n=42)	Control (n=42)	P value cupressure compared to control	P-value acupressure compared to placebo
Incidence of Vomiting & Retching n (%)	28 (67)	32 (76)	30 (71)	p= 0.6369	p= 0.3340
The mean number of acute emetic episodes	2.23 (1.25)	2.5 (1.81)	2.25 (1.94)	p= 0.9050	p= 0.1107
Incidence of acute nausea n (%)a dichotomous fashion	26 (62)	30 (71)	30 (71)	p= 0.3545	p= 0.3545
Accumulative incidence of nausea>3(0-6 scale)in the first 24hs of chemotherapy	18(43)	28(67)	24(57)	P= 0.01904	P= 0.0284
Nausea severity (0-6 scale) in first 24 hours after chemotherapy Mean (SD)	1.62 (2.04)	2.17 (2.09)	1.64 (1.99)	p= 0.8967	p= 0.0006

No significant differences were found in the incidence of acute nausea or emesis 24- h following chemotherapy by treatment groups. Significant difference was found in the severity of early nausea (0-6 scale) in the acupressure group M (SD) 1.62 (2.04) as compared to placebo group 2.17 (2.09), p=0.0006. (Table 4.3)

No significant differences in the incidence of acute vomiting & retching were found by treatment group 67% (28/42) in acupressure group

and 76% (32/42) in the placebo group (p= 0.6369) and (p=0.3340) compared to control group 71% (30/42) respectively). The mean (SD) number of acute emetic episodes in acupressure group 2.23 (1.25), p= 0.9050, placebo 2.50 (1.81) p=0.1107 compared to control 2.25 (1.94) respectively (Table 4.3).

So no significant difference of the mean number of acute emetic episode was seen between the groups.

Delayed vomiting: The results are accumulating covering the entire period:

Table (4.4): Incidence of delayed vomiting episodes: Days 2-5, n (%) in the three groups after chemotherapy

Vomiting days 2-5 Incidence of vomiting	Acupressure (n=42)	Placebo (n=42)	Control (n=42)	p-value acupressure compared to control	p-value acupressure compared to placebo	p-value placebo compared to control
Day 2	17 (40)	20 (48)	14 (33)	P=0.4976	P=0.5097	P=0.1823
Day 3	17 (40)	25 (60)	18 (43)	P=0.8248	P=.0809	P=0.1265
Day 4	9 (21)	14 (33)	12 (29)	P=0.4497	P=0.2212	P=0.6369
Day5	6 (14)	7 (17)	10 (24)	P=0.2664	P=0.7629	P=0.4152
The whole period	20 (48)	27 (64)	24 (57)	p= 0.3822	p= 0.1239	p= 0.5027

The incidence of delayed vomiting episodes days 2-5 was 48% (20/42), 64% (27/42), and 57% (24/42) in the acupressure, placebo and control group respectively. No significant differences were found between the groups during the whole period. (Table 4.4)

Delayed nausea: The results are accumulating covering the entire period:

Table (4.5):Comparison between the three groups for the day 2-5 after chemotherapy.

Mean (SD) Of delayed nausea severity (0-6 scale) patients ≥ 0	Acupressur (n=42)	Placebo (n=42)	Control (n=42)	P-value Acupressure vs control	P-value Acupressure vs placebo	P-value Placebo Vs control
Day 2						
Morning	1.43 (2.01)	1.57(1.83)	2.33 (2.02)			
12:00	1.85 (2.05)	1.57 (1.87)	2.09 (1.97)			
18:00	1.80 (2.14)	1.40 (1.72)	2.30 (1.89)			
Before sleep	1.87 (2.06)	1.52 (1.82)	1.88 (1.90)			
Total Mean (SD)	1.73 (1.56)*	1.51 (1.87) †	2.75 (1.94)* †	p= 0.0000	p= 0.1526	p= 0.0000
Day 3						
Morning	1.56 /1.98)	1.59 (1.87)	2.30 (2.10)			
12:00	1.87 (2.09)	1.40 (1.87)	2.38 (2.08)			
18:00	1.68 (2.04)	1.40 (1.83)	2.09 (2.05)			
Before sleep	1.87 (2.19)	1.21 (1.81)	2.02 (2.07)			
Total Mean (SD)	1.74 (2.07) *,**	1.39(1.84)*	2.19(2.07) *†	p= 0.0000	p= 0.0214	p= 0.0000
Day 4						
Morning	1.51 (1.81)	1.54 (1.84)	1.88 (1.96)			
12:00	1.39 (1.74)	1,23 (1.73)	2.04 (2.07)			
18:00	1.31 (1,66)	1.16 (1.72)	1.78 (1.84)			
Before sleep	1.31 (1.73)	1.07 (1.62)	1.52 (1.77)			
Total Mean (SD)	1.37 (1.73)*	1.25 (1.72) †	1.80(1.91)* †	p= 0.0049	p= 0.4017	p= 0.0003
Day 5						
Morning	1.07 (1.61)	1.33 (1.83)	1.61 (1.80)			
12:00	0.97 (1.47)	1.19 (1.81)	1.40 (1.75)			
18:00	0.97 (1.58)	1.09 (1.69)	1.33 (1.81)			
Before sleep	0.97 (1.65)	1.14 (1.63)	1.23 (1.58)			
Total Mean (SD	**0.99 (1.57)***	**1.18 (1.74)**	**1.39 (1.73)***	p= 0.0000	p= 0.1541	p= 0.1395
The whole period (2-5 days) Total mean (SD	1.45 (1.73)*	1.33(1.66) †	2.03 (1.91)* †	p= 0.0002	p= 0.4116	p= 0.0010

*P < 0.05 when P6 acupressure is compared to control group.

**P< 0.05 when P6 acupressure is compared to placebo group.

† P< 0.05 when placebo is compared to control group.

Further analyses indicated that significant difference existed in the intensity of delayed nausea by acupressure group, mean (SD) 1.45 (1.73), p= 0.0002 as compared to control 2.03 (1.91)for the whole period. Significant difference also existed in the intensity of delayed nausea by placebo group mean (SD) 1.33 (1.66), p=0.0010 as compared to control 2.03 (1.91), here we noted a placebo effect (Table 4.5).

Table (4.6): Incidence of delayed nausea Days 2-5 in the three groups.

Incidence of delayed nausea day 2-5 Patients who answers yes	Acupressure (n=42)	Placebo (n=42)	Control (n=42)	P-value Acupressure vs control	P-value Placebo vs control
Day 2	25 (60)	24(57)	32 (76)	p= 0.1020	p= 0.0641
Day 3	24(57)	21(50) †	32(76) †	p= 0.0641	p= 0.0129
Day 4	22(52)*	22(52) †	31(74)* †	p= 0.0419	p= 0.0419
Day 5	17 (40)*	18(43)	26 (62)*	p= 0.0495	p= 0.0805
The whole period	17 (40)*	18 (43)	26(62)*	p= 0.0495	p= 0.0805

*P < 0.05 when P6 acupressure is compared to control group.

† P< 0.05 when placebo is compared to control group.

The acupressure group had a statistically significant reduction in the incidence of delayed nausea 40% (17/42) as compared to the control group 62% (26/42) (p= 0.0495) ((Table 4.6).

Table (4.7): Accumulative incidence of delayed nausea Days 2-5 ≥ 3 (0-6 scale) of moderate to very severe nature in the three groups.

Delayed nausea Day 2-5 ≥3 (0-6 scale)	Acupressure n=42	Placebo n=42	Control n=42	P-value Acupressure vs control	P-value Placebo vs control
Day 2	18 (43)*	18 (43) †	28 (67)* †	p= 0.0284	p= 0.0284
Day 3	17 (40)	16)38)	22 (52)	p= 0.2740	p= 0.1884
Day 4	14 (33)*	13 (31)†	23 (55)* †	p= 0.0479	p= 0.0275
Day5	7 (17)*	12 (29)	18 (43)*	p= 0.0087	p= 0.1719
The whole period days 2-5	23 (55)*	22 (52) †	33 (79)*†	p= 0.0206	p= 0.0116

*P < 0.05 when P6 acupressure is compared to control group.

**P< 0.05 when P6 acupressure is compared to placebo group.

† P< 0.05 when placebo is compared to control group.

The percentage of the patients who had delayed moderate to very severe nausea day 2-5 (≥ 3 on 0-6 scale) in the acupressure group is 55% (23/42) (p= 0.0206), in the placebo group 52% (22/42) (p= 0.0116), a statistically significant reduction existed as compared to control 79% (33/42), here we noted as a placebo effect (Table 4.7)

Delayed emetic episodes: The results are accumulating covering the entire period:

Table (4.8): Number of delayed emetic episodes Days 2-5in the three groups. Values given as Mean (SD)

Mean (SD no. of emetic episodes The patients who vomited only are included	**Acupressure (n=42) Mean (SD)**	**Placebo (n=42) Mean (SD)**	**Control (n=42) Mean (SD)**	p-value acupressure vs control	p-value acupressure vs placebo	p-value placebo vs control
Day 2						
Morning	1.5 (0.83)	1.78 (1.11)	2.45 (1.5)			
12:00	1.5 (0.83)	2.1 (1.44)	2.57 (1.38)			
18:00	2 (0.98)	2 (1.32)	2.27 (1.34)			
Before sleep	1.8 (0.91)	2 (1.16)	2.3 (1.10)	P=	P=	P=
Total	1.7 (0.88)	1.97(1.25)	2.39 (1.33)	0.0000	0.0907	0.0117
Day 3						
Morning	1.75 (0.92)	1.46 (0.839	2.38 (1.54)			
12:00	1.75 (0.99)	1.83 (1.05)	2.33 (1.37)			
18:00	2.22 (1.18)	1.46 (0.86)	3,00 (1.53)			
Before sleep	2.4 (1.30)	1.71 (0.81)	2.28 (1.15)	p=	p=	p=
The whole period	2.03 (1.09)	1.61 (0.88)	2.49 (1.39)	0.0035	0.0058	0.0000
Day 4						
Morning	1.12(0.51)	1.66 (0.76)	2 (1.21)			
12:00	1.40 (0.56)	1.33 (0.52)	2.33 (1.24)			
18:00	1.8 (0.73)	1.37 (0.61)	2.33 (1.19)			
Before sleep	1.66 (0.83)	1.6 (0.76)	2.66 (1.20)			
	1.49 (0.65)	1.49 (0.66)	2.33 (1.21)	p=	p=	p=
The whole period				0.0000	1.0000	0.0000
Day 5						
Morning	1.25 (0.43)	1.66 (0.85)	1.8 (1.08)			
12:00	1.66 (0.79)	1.66 (0.45)	2.33 (1.12			
18:00	1.5 (0.57)	1.00 (0.51)	2.04 (2.33)			
Before sleep	0.21 (0.57)	1.00 (0.51)	2.2 (1.01)	p=	p=	p=
The whole period	1.5 (0.64)	1.33 (0.58)	2.09 (1.13)	0.0001	0.2327	0.0000
The whole period 2-5 day	1.68 (0.86)*	1.6 (0.82)†	2.07(1.20)* †	p= 0.0109	p= 0.5900	p= 0.0020

*$P < 0.05$ when P6 acupressure is compared to control group.

† P< 0.05 when placebo is compared to control group.

The mean of number of delayed emetic episodes days 2-5 was significantly less in the acupressure group mean (SD) 1.68 (0.86) as compared to control 2.07(1.20) p=0.0109 and less in the placebo group 1.6 (0.82) as compared to control P= 0.0020 (Table 4.8).

Requirement of rescue antiemetic:

Table (4.9): Requirement of rescue antiemetic in the three group's days 1-5

The whole period	Acupressure (n=42)	Placebo (n=42)	Control (n=42)	P- value Acupressure vs control	p-value placebo vs control
`Not required antiemetic	19	16	10	p=0.0389	p= 0.1568
Required antiemetic	23 (55)*	26 (62)	32 (76)*	p= 0.0389	p= 0.1568

*P < 0.05 when P6 acupressure is compared to control group.

Requirement of rescue antiemetic was significantly lower in P6-acupressure (55%, 23/42), as compared to control group (76%, 32/42) (p= 0.0389) (Table 4.10).

Analyses of QOL by using FACT-G. The results are accumulating covering the entire period:

Table (4.10): Comparison of the study outcomes by Analyses of QOL by using FACT-G

FACT-G (version 4)	Acupressure (n=42)	Placebo (n=42)	Control (n=42)	P value Acupressure vs control
Physical well-being (PWB)	16	15	15	
Social/family wellbeing SWB)	24	20	19	
Emotional well-being EWB)	16	15	17	
Functional well- being (FWB)	18	17	18	
over all QOL score 108 point	74	67	69	p= 0.4720

Exploratory analyses of QOL by using FACT-G was shown that no statistically significant differences between groups were observed for the overall items response rate of the FACT-Scale which were 74/108, 67/108, 69/108 in the acupressure, placebo and control group respectively (Table 4.10). The FACT-Scale is considered to be an acceptable indicator of patient QOL as long as overall item response rate is greater than 80%.

Overall patient satisfaction and recommendations for other patients to wear acupressure bands:

Table (4.11): Overall patients´ satisfaction with acupressure and if they would recommend other patients to wear bands when receiving chemotherapy.

	Acupressure (n=42)	**Placebo (n=42)**	**P-value 0.05**
Satisfaction with P-6 acupressure (0-6 scale) n (%) ≥ 3	35 (81)*	27(64)*	p= 0.0471
Recommendation P-6 acupressure (0-6 scale) ≥ 3	34 (79)*	26 (62)*	p= 0.0533

*$P < 0.05$ when P6 acupressure is compared to control group.

The patients were satisfied with the antiemetic treatment in (P6-acupressure, and placebo-acupressure). The percentage of the patients (≥ 3 on 0-6 scale) who were satisfied with treatment was 81% (35/42) in the P6-acupressure group, and 64% (27/42) in the placebo group (p= 0.0471). Percentage of the patients who would recommend acupressure treatment was 79% (34/42) in the P6-acupressure group, and 62% (26/42) in the placebo group (p= 0.0533). (Table 4.11)

Chapter Five

Discussion

5.1 Methods Discussion

5.1.1 The placebo effect

It may be possible that treatment in the placebo point prompted non-specific effect. Patients were not informed of the use of a "sham" point, but the patients were informed that a comparison of the two "different" points will be performed. The placebo effect of acupressure can not be underestimated as long as we are researching on human being. Dundee was confirmed that the effect of the P6 point acupuncture in controlling chemotherapy-related nausea and vomiting is bigger than placebo or sham acupuncture (Dundee *et al*., 1989, 1991). Although we acknowledge the difficulties the placebo effect makes in this type of investigation, we believe that there was positive response to acupressure in the group that was agreeable to it. This response can not be ignored.

5.1.2. The three groups design

A homogeneous sample was used in the current study in which all participants have the same sex (female) had the same diagnosis (breast cancer), and received the same chemotherapeutic agents (doxorubicin). A three-group design was used to estimate the number of control events, i.e., incidence, without any intervention. This is crucial when discussing the benefits of prophylactic treatment (Trams 2001; Part II). The three groups design also gives a real appreciation of the placebo effect.

The active stimulation (Sea Band ®) at a point that is not an accupoint was used. Sea Band ® covered with a bandage so that their condition should not be obvious to care providers, but we could not exclude the possibility that stimulation of non-acupoint choose on the back of the forearm could have stimulated the meridians connected to the P6-acupoint. Blinding is used to eliminate bias (Day and Altman, 2000).

In Oncology study P6-acupressure was effective as anti-emetics only if given before chemotherapy (Dundee and Milligan, 1988 b). With Sea-Band ® applies a constant pressure, eliminating the need for repeated stimulation (Barsoum *et al*., 1990). The studies give different ideas and we do not know yet whether it is better to stimulate two or forearm as a bilateral stimulation (Ho et al., 1996; Stein et al., 1997), dominant (Dundee and Milligan 1988 b) and right forearm stimulation was studied (Harmon *et al.*, 1999) and effect of unilateral stimulation has been reported (Lee and Ready, 1999; Vickers, 1996).

5.1.3 Endpoint measured

It is important to distinguish between two phenomena that vomiting is a relatively clear physiological endpoint, and nausea is not (Morrow, 1984). There is no standard method for measuring the intensity of nausea and lack of consensus on the degree of symptoms are clinically significant (Apfel *et al*., 1998).

Nausea and vomiting is not an all or nothing event. If an individual patient has suffered from very severe NV in the past, although the reduction can be a success (Eberhart *et al.*, 2000 b). Patient assessment of

antiemetic efficacy based on changes in self-reported nausea (Bonne Terre *et al*., 1991).

5.1.4 Instruments

MANE (Morrow Assessment of nausea and vomiting) (Morrow, 1984) was used in the assessment of symptoms such as nausea. Severity of the symptom was rated on the scale (0-6), 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = difficult, 5 = very severe and, 6 = unbearable. MANE has been validated clinically, and a test-retest reliability coefficient has been determined (Morrow, 1984).

QOL was assessed using the Functional Assessment of Cancer Therapy Scale-General (FACT-G). It is used internationally and has undergone extensive psychometric testing: test/retest reliability coefficients range from 0.82 to 0.92, internal consistency of subscales measures range from 0.60 to 0.89) (Ward, 1999).

Nausea and vomiting were measured by a patient report diary developed for this purpose by (Burish *et al*., 1987; Carey and Burish, 1988)

5.1.6. Why acupressure

Clinical trials of chemotherapy patient's show that the protective affect of P6 stimulation of acupuncture on chemotherapy illness last about 8 hours (Dundee, 1988). The inconvenience of applying acupuncture at regular intervals during chemotherapy has generated interest in the more convenient stimulation techniques such as non-invasive electrical stimulation, or acupressure.

5.2. Results Discussion

Findings from the present study confirmed that acupressure is efficacious for control of delayed chemotherapy related nausea and emesis and is a value-added method in addition to pharmaceutical management for women undergoing treatment for breast cancer. This is in accordance with the accumulating body of evidence related to acupressure during chemotherapy and shows that acupressure is a safe and complementary option in the management of chemotherapy-related nausea and vomiting (Roscoe *et al*., 2002, Roscoe *et al*., 2005; Shin *et al*., 2004; Dibble, 2000).

Our study is consistent with the study results of Dibble *et al* (2000) which were shown that finger acupressure may decrease nausea among women undergoing chemotherapy for breast cancer. Our study is also in agreement with the study of Roscoe *et al* (2006) who showed that acupressure wrist bands were efficacious and may be appropriate form of adjuvant therapy for nausea management for breast cancer patients, especially those who are most at risk for experiencing severe nausea following chemotherapy treatment

5.2.1. Acute nausea

Significant difference was found in the severity of early nausea (0-6 scale) at the first day in the acupressure group M (SD) 1.62 (2.04) as compared to placebo group 2.17 (2.09), p= 0.0006 which is consistent with **t**he study of Nyström *et al* (2008) who demonstrated that acupuncture treatment in cancer patients can be associated with a significantly reduced intensity of nausea during a period of chemotherapy in their final phase of life.

The largest study of acupressure use for chemotherapy-related nausea and vomiting (n = 739) to date showed that the use of antiemetic pills was lower in the acupressure group (mean pills = 5.1) compared to the control group (mean pills = 9.7). This result is in agreement with the result of our present study regarding the requirement of rescue anti emetics which was significantly lower in P6-acupressure (55%, 23/42), compared to control group (76%, 32/42) (p= 0.0389). However, there were some key differences between this study and our study in that some patients in the latter study received cisplatinbased chemotherapy, which is considerably more emetogenic and difficult to manage than the types of chemotherapy used in the present study. Also, the Roscoe et al. Study (Roscoe, 2003) used patients with different cancer diagnoses, hence it was not as homogeneous as our study. It also seemed that their patients used mainly dexamethasone/other corticosteroids for the management of delayed nausea and vomiting whereas all of our patients received dexamethasone once. It is well known that dexamethasone is highly effective in managing delayed nausea and vomiting, although many clinicians, are sceptical of the use of steroids for prolonged periods of time. Hence, the use of dexamethasone may have contributed to the better control of nausea and vomiting in the study by (Roscoe *et al*., 2003), minimising the possible effect of wrist Bands. Such use of dexamethasone is a key factor to consider in future antiemetic trials of this kind.

In our study, no significant differences were found in the incidence of acute nausea or emesis 24- h following chemotherapy by treatment groups. This is inconsistent with the pooled results of 11 randomized controlled trials evaluating acupuncture-point stimulation plus antiemetic for chemotherapy-induced nausea and vomiting showed a significant

reduction in the proportion of patients experiencing acute vomiting (Esso *et al*., 2005). On the other hand, in the current study acupressure seems to reduce chemotherapy-induced acute nausea severity, a significant difference was found in the severity of early nausea (0-6 scale) in the acupressure group M (SD) 1.62 (2.04) as compared to placebo group 2.17 (2.09), p= 0.0006, this is consistent partially with the study of Ezzo *et al* (2005) who showed a marginal statistical significance for reducing Severity of acute nausea.

Although other studies have also shown positive (and negative) effects with the use of acupressure in managing chemotherapy-induced nausea and vomiting, they are not easily comparable with the current study, as the method of acupressure differed. Past studies have used either finger acupressure and use of more than the P6 point, 24 palliative care populations (Dundee *et al*., 1991), or use of the Relief band / transcutenuous electrical nerve stimulation at the P6 point (Pearl, 1999, Treish *et al*., 2003; Roscoe *et al*., 2005). Mixed chemotherapy protocols and antiemetics used also make comparisons difficult. Furthermore, in another study by Roscoe *et al* (2005), where gender and type of chemotherapy were controlled, the placebo control group used an active Wrist Band, which may have led to the negative findings reported. It may be that constant pressure on the P6 point (as in the acupressure Wrist Bands) may produce better results than pressing the stud only or using electrical nerve stimulation to the point (as in the Relief Band).

5.2.2. Acute vomiting

In the current study, no significant differences were found in the incidence of acute emesis 24- h following chemotherapy by treatment

groups. This finding is consistent with Dundee and Yang (1990) found that acupressure, by itself, was not sufficient to prevent vomiting in chemotherapy patients. Our results also are in agreement of Roscoe *et al* (2005) who did not show that acupressure bands were efficacious when used as an adjunct to pharmacological anti emetics for the control of the incidence of chemotherapy-related vomiting in female breast cancer patients.

5.2.3. Delay nausea

Incidence of delayed nausea was significantly different among groups, with 55% of the acupressure group, 52% of the placebo group, and 79% of the control group $p<0.05$). Both the true acupressure and placebo acupressure groups were significantly different from the control group. Our results are consistent with study results of Ferrara-Love *et al*., 1996.

Patients randomized to the acupressure group had significantly less delayed nausea on (Days 2–5) of treatment than patients in the control. This reduction in nausea, however, did not extend to the acute phase following treatment (Day 1), nor was there a reduction in emesis. It cannot be ascertained from our data why the bands were helpful on (Days 2–5) of treatment but not on the first day. It may be related to the fact that the acute and delayed treatment-related nausea have different etiologist. So our results were not consistent with the study of (Roscoe *et al.*, 2003).

Our results are consistent with the results of Pearl and colleagues (1999) who examined the efficacy of acustimulation in 42 patients in a randomized, double-blind, placebo- controlled crossover trial, with a follow-up. For the 18 patients who completed the crossover component of

the study, patients in the active band cycle, as compared to the placebo band cycle, reported a significantly lower severity of nausea during the second through fourth post-treatment days (O`Brien *et al*., 1996). Our results are consistent with the results of study there acupuncture combined with antiemetic which can effectively decrease the incidence and degree of cisplatin-induced delayed nausea and vomiting (Sima & Wang, 2009)

5.2.4. Delayed emesis

Our results regarding the mean number of delayed emetic episodes days 2-5 was significantly less in the acupressure group M (SD) 1.68 (0.86) as compared to control 2.07(1.20,) p=0.0022 and less in the placebo group 1.6 (0.82 as compared to control, 2.07(1.20) P= 0.0005. This result is consistent with the study of Shen et al (2000) which showed that the number of emesis episodes occurring during the 5 days was lower for patients receiving electro acupuncture compared with those receiving minimal needling or pharmacotherapy alone?

Patients in both groups reported substantially lower rates of delayed nausea compared to patients in the control group, thereby indicating the presence of a powerful placebo effect. This is in consistent of our study (Alkaissi,1999) of PONV which had a similarly-designed 3-arm acupressure band study of 60 patients undergoing minor outpatient gynaecological surgery also we reported positive results for placebo bands (Alkaissi,1999). Patients randomized to both the active acupressure band condition and to the placebo band condition had significantly less postoperative nausea than patients randomized to the no band control group (P= 0.05). There were no differences in the amount of nausea reported between the two acupressure band groups (Alkaissi, 1999).

In the current study no significant differences were found between the groups in the incidence of delayed vomiting episodes day 2-5, this was consistent with other studies in which no significant differences were found between the groups and delayed symptoms remain a problem for many cancer patients (Dibble 2003, 2004, Roscoe *et al*., 2005)

5.2.5. Quality of life

Nausea has obvious consequences on the quality of life, and it is not unusual for patients to experience nausea as a greater problem than pain (Strang *et al*., 1999). Therefore expert panels (Gralla *et al*., 1999; Hesketh et al., 1998) emphasize the need for additional ways to reduce symptoms. Chemotherapy induced nausea and vomiting can impair a patient's quality of life **(**Osoba, 1997**),** cause emotional distress, (Love *et al*., 1989**)** and aggravate cancer-related symptoms

In our study, no statistically significant differences between groups were observed for the overall items response rate of the FACT-Scale which were 74/108, 67/108, 69/108 in the acupressure, placebo and control group respectively which is inconsistent with the other study which showed that psychological well-being improved in women with breast cancer randomized to treatment with either applied relaxation and electro-acupuncture. On the other hand, our study is in complete agreement with the findings of Roscoe *et al* (2005)

5.2.6. The strength of the study

The strengths of the study include the use of a homogeneous group receiving the same antiemetics for acute nausea and vomiting, control of patient clinical and demographic characteristics (i.e. chemotherapy type,

susceptibility to nausea or vomiting), and a prospective assessment of nausea and vomiting experience using a validated and widely used scale. The use of a placebo acupressure point as one group in the current study strengthens the hypothesis that the results are not merely because of a placebo effect.

Chapter Six

Conclusion& Recommendation

6.1 Conclusion

We conclude that acupressure showed benefit for delayed nausea and the mean number of delayed emetic episodes, but not for the incidence of delayed vomiting, early vomiting or for acute nausea

Acupressure, there for, may offer an inexpensive, convenient, self-administered intervention for patient on chemotherapy to reduce nausea and vomiting at home on 2-5 days of chemotherapy.

It is not clear why acupressure was effective for delayed nausea and not the incidence of delayed vomiting, but some trials for other kinds of nausea and vomiting have produced the sham outcome. It may be that, to influence vomiting, stronger form of P6 stimulation is needed. Acute nausea remains a problem even with the use of current antiemetic. It is not known why acute symptoms are so difficult to treat with conventional medications, but it is apparent that acupressure affects little for acute nausea.

6.2 Recommendation

P6- Acupressure is well-tolerated and effective as an adjunct in reducing chemotherapy-related nausea. Based on our results, we conclude that P6-acupressure, as an addition to standard, modern antiemetic therapy, has reduced delayed emesis in female patients undergoing doxorubicin-based chemotherapy. It is an alternative means of therapy aside from conventional or expensive antiemetic drugs and this is worthy of further

investigation. The results of this study concur with that of other randomized controlled trials which showed that acupuncture-point stimulation reduced the proportion of patients experience in chemotherapy-induced vomiting.

Acupressure is easily learnt and taught and patients should be informed about its potential role and taught how to apply it. Leaflets about acupressure for the management of nausea and vomiting could be available in chemotherapy units so that patients who are interested to use such a technique are encouraged to come forward and learn more from nurses or other health professionals. This can add to the patients' options of their antiemetic approaches and empower them to be involved in the management of these distressing side effects.

Acupressure offers a no-cost, convenient, self-administered intervention for chemotherapy patients to reduce acute nausea. Acupressure devices (i.e., Wrist Bands, travel bands, acupressure bands) have been developed to provide passive acupressure on P6. Acupressure can be administered by healthcare providers, family members, or patients themselves (Gottlieb; Porkert & Ullman, 1988) and does not involve puncture of the skin.

Implications for Oncology Nurses

Studies about acupressure have concluded that acupressure is an important adjunct to pharmaceuticals in managing CINV (Dibble et al., 2000; Shin et al., 2004). Those studies as well as the current study suggest that oncology clinicians can include acupressure in their list of options for the management of CINV, especially delayed nausea and vomiting.

Specific recommendations provided by oncology nurses are not only useful but also are very appreciated by patients.

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Appendix A

1. Functional Assessment of Cancer Therapy-G (FACT-G) (Cella 1993)

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix B
FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) LICENSING AGREEMENT

from FACIT.org
June 30, 2009

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FACIT.org
381 S. Cottage Hill Avenue
Elmhurst, IL 60126
USA
www.FACIT.org

Appendix C
Patient self assessment tool (questionnaire)

(-------)

الكتاب اليومي

التقييم الذاتي للمرضى

Diary book

Patient self assessment tool

(القيء والغثيان الناتج عن العلاج الكيماوي)

الاسم:----------

معلومات للمريضة التي تشملها الدراسة

من الممكن أن تتعرض المريضة للقيء والغثيان بعد أخذها للعلاج الكيماوي وهذه من الآثار الجانبية للعلاج مما يؤثر سلبيا على الحياة العامة للمريضة.

لذلك تهدف هذه الدراسة إلى تخفيف هذه الآثار وذلك عن طريق استعمال الأساور المطاطية الضاغطة وقد أثبتت التجارب الفعالية الجيدة لهذه الطريقة.

إن مشاركتك في هذه الدراسة سوف تكون باختيارك وعن طريق القرعة تقسم المشاركات إلى ثلاث مجموعات.

المجموعة الأولى ,المجموعة الثانية المجموعة الثالثة.

وخلال هذه التجربة سوف تقومين بتعبئة عدة نماذج مهمة لإتمام هذه الدراسة ,هناك نموذج يحتوي على بيانات شخصية سوف تقوم الممرضة في قسم العلاج الكيماوي بمساعدتك بتعبئته,كذلك تقوم الممرضة بتوضيح كيفيـــة تعبئتك للنماذج الأخرى والتي سيتم تعبئتها في البيت في اليوم الأول إلى اليوم الخامس من أخذك ألعلاج .كذلك سيتم توضيح طريقة لبس الأساور .نأمل منك إعادة المغلف ودفتر النماذج ,والأساور بعد الانتهاء.

وشكراً

في حالة وجود إي استفسار يمكن الاتصال على إحدى الأرقام

د.عائدة أبو السعود القيسي 0599589407

زائدة نصار 0599389223

البيانات الاجتماعية

أرجو من حضرتك الإجابة على هذه المعلومات بتظليل المربع المناسب ,من اجل استخدامها لإتمام هذه الدراسة

الاسم----------:العمر----------:

اسم العلاج الكيماوي المستخدم----------:-1الجرعة ----------طريقة الإعطاء----

---------- -2

---------- -3

اسم الدواء المستخدم لمنع القيء----------1الجرعة----------طريقة اخذ ألد واء-----

-

----------2 الجرعة ----------طريقة اخذ الد واء

البيانات الاجتماعية:					
الحالة الاجتماعية	عزباء	متزوجة	أرملة	مطلقة	
الأطفال /هل لديك أطفال؟	نعم -----	لا	عدد الأطفال------		
المسكن /تسكنين؟	وحدك	مع الشريك	مع الأسرة الأم	غير ذالك ---	
التعليم /حددي أعلى مستوى	ابتدائي	ثانوي	جامعة	دراسات عليا	غير ذالك حددي
الحالة المهنية	وظيفة بدوام كامل	وظيفة بدوام جزئي	غير موظفة	ربة بيت	طالبة
الحالة الصحية	بدون إمراض مزمنة	أمراض مزمنة	حددي-------		
هل أصابك قيئ إثناء الحمل ؟	نعم	لا			
هل أصابك غثيان أثناء الحمل؟	نعم	لا			
هل تعانين من الغثيان أثناء ركوبك حافلة نقل / سيارة / باص-----	نعم	لا			
هل تعانين من القيء أثناء ركوبك حافلة نقل؟	نعم	لا			
هل تعانين من القي أثناء فترة الحيض؟	نعم	لا			
هل تعانين من الغثيان أثناء فترة الحيض؟	نعم	لا			

تعبأ هذه الاستمارة في **اليوم الأول** من أخذك للعلاج الكيماوي حسب الساعات التالية

استمارة رقم (1)

خـــــلال فتـــــرة العلاج	الثانية عشرة ظهرا	السادسة مساءا	قبل النوم
هـــل تقيـــأت ؟ نعـــم لا عدد المرات --- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان شدة الغثيان 1------2-----3-----4-----5------6 هل أصابك تجشؤ؟ نعم لا	هـــل تقيـــأت ؟ نعـــم لا عدد المرات ------- هل أصابك غثيان؟ نعم لا في حال نعم حـــددي شدة الغثيان شدة الغثيان 1------2-----3-----4-----5------6 هل أصابك تجشـــؤ؟ نعم لا	هـــل تقيـــأت ؟ نعـــم لا عدد المرات ------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان شدة الغثيان 1------2-----3-----4-----5------6 هل أصابك تجشؤ؟ نعـــم لا	هل تقيأت ؟ نعم لا عدد المرات ---- -- هل أصابك غثيان؟ نعم لا في حال نعم حـــددي شـــدة الغثيان شدة الغثيان 1------2-----3-----4-----5------6 هل أصابك تجشـــؤ؟ نعـــم لا

حيث أن (1)تعني غثيان خفيف جدا

(2) تعني غثيان خفيف

(3) تعني غثيان متوسط

(4) تعني غثيان شديد

(5) تعني غثيان شديد جدا

(6) تعني غثيان لا يمكن احتماله

التجشؤ :هو محاولة التقيؤ بدون خروج أي شيء من محتويان المعدة

حددي عدد مرات تناولك للأدوية المضادة للقيء والغثيان ---------- .

استمارة رقم(2)

تعبا هذه الاستمارة في اليوم الثاني لأخذك العلاج الكيماوي

حوالي السادسة صباحا	الثانية عشرة ظهرا	السادسة مساءا	قبل النوم
هل تقيأت ؟ نعم لا عدد المرات ------ هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1-----2-----3-----4--- --5---6 هل أصابك تجشؤ؟ نعم لا	هل تقيأت ؟ نعم لا عددا لمرات ------ هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1-----2-----3----4--- -5----6 هل أصابك تجشؤ؟ نعم لا	هل تقيأت؟ نعم لا عدد المرات --------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1-----2-----3----4--- -5----6 هل أصابك تجشؤ؟ نعم لا	هل تقيأت؟ نعم لا عددا لمرات ------ هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1-----2----3----4-- --5----6 هل أصابك تجشؤ؟ نعم لا

حددي عدد مرات تناولك للدواء المضاد للقيء والغثيان----------

تعبا هذه الاستمارة في اليوم الثالث لأخذك العلاج الكيماوي

استمارة رقم(3

حوالي السادسة صباحا	الثانية عشرة ظهرا	السادسة مساءا	قبل النوم
هـــــل تقيـــــأت؟نعم لا عددا لمرات ------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان ---4----3----2-----1 6----5-- هل أصابك تجشؤ؟ نعم لا	هـــل تقيـــأت ؟ نعـــم لا عددا لمرات -------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان ---4----3----2-----1 6----5-- هل أصابك تجشؤ؟ نعم لا	هـــل تقيـــأت ؟ نعـــم لا عددا لمرات -------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان ---4----3----2-----1 6----5- هل أصابك تجشؤ؟ نعم لا	هل تقيأت؟ نعم لا عددا لمرات ------- هل أصابك غثيان؟ نعم لا. في حال نعم حددي شدة الغثيان --4----3-----2----1 6----5-- هل أصابك تجشؤ نعـــم لا

حددي عدد مرات تناولك للدواء المضاد للقيء والغثيان----------

تعبا هذه الاستمارة في اليوم الرابع لأخذك العلاج الكيماوي حسب الساعات التالية

استمارة رقم(4)

حوالي السادسة صباحا	الثانية عشرة ظهرا	السادسة مساءا	قبل النوم
هل تقيأت ؟ نعم لا عددا لمرات-------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1------2-----3-----4--- 6------5-- هل أصابك تجشؤ نعم لا	هل تقيأت ؟ نعم لا عددا لمرات -------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1------2-----3----- 4-----5------6 هل أصابك تجشوء نعم لا عدد المرات--------	هل تقيأت؟ نعم لا عددا لمرات--------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1------2-----3---- 4-----5-----6 هل أصابك تجشؤ؟ نعم لا عدد المرات--------	هل تقيأت ؟ نعم لا عددا لمرات ------- هل أصابك غثيان؟ نعم لا في حال نعم حددي شدة الغثيان 1------2-----3-----4- ----5-----6 هل أصابك تجشؤ؟ نعم لا عدد المرات--------

حددي عدد مرات تناولك للأدوية المضادة للقيء والغثيان---------- .

تعبا هذه الاستمارة في اليوم الخامس لأخذك العلاج الكيماوي

استمارة رقم(5)

حوالي السادسة صباحا	الثانية عشرة ظهرا	السادسة مساءا	قبل النوم
هل تقيأت اليوم؟ نعم لا عددا عدد المرات----------	هل تقيأت اليوم؟ نعم لا عدد المرات ---------	هل تقيأت اليوم؟ نعم لا عددا لمرات -------	هل تقيأت اليوم؟ نعم لا عددا لمرات --------
هل أصابك غثيان؟ نعم لا	هل أصابك غثيان؟ نعم لا	هل أصابك غثيان؟ نعم لا	هل أصابك غثيان؟ نعم لا
في حال نعم حددي شدة الغثيان --4-----3-----2------1 6-----5--- هل أصابك تجشؤ؟ نعم لا	في حال نعم حددي شدة الغثيان ---4-----3-----2------1 6-----5-- هل أصابك تجشؤ؟ نعم لا	في حال نعم حددي شدة الغثيان -----4-----3-----2------1 6------5 هل أصابك تجشؤ؟ نعم لا	في حال نعم حددي شدة الغثيان --4-----3-----2------1 6------5--- هل أصابك تجشؤ؟ نعم لا

حددي عدد مرات تناولك للأدوية المضادة للقيء والغثيان---------- .

استمارة مدى رضا المريضة

عن طريقة العلاج المستخدم للوقاية من القيء والغثيان بعد اخذ العلاج الكيماوي

استمارة رقم (6)

سوف تقومين بالإجابة على هذه الاستمارة في اليوم الخامس من أخذك للعـــلاج الكيمـــاوي إي اليـــوم الأخيـــر للدراسة.

نود إن تقومي بتقييم مدى رضاك عن الطريقة المستخدمة للوقاية من القيء والغثيان)لبس الأســـاور المطاطيـــة الضاغطة (وسيكون التقييم من صفر إل ستة.

حيث إن صفر :غير راضية

ستة :راضية كثيرا

0------1-------2--------3--------4---------5---------6

هل ستقترحين على الآخرين استعمال طريقة الأساور المطاطية للوقاية من القيء والغثيان بعـــد اخـــذ العـــلاج الكيماوي.

0--------1--------2---------3--------4---------5---------6

أقوم بالاقتراح بالتأكيد لن أقوم بالاقتراح مطلقا

حيث إن ستة :سوف أقوم بالاقتراح بالتأكيد

صفر :لن أقوم بالاقتراح مطلق

جامعة النجاح الوطنيّة

كليّة الدراسات العليا

مدى تأثير ألأساور الضاغطة في منع القيء والغثيان عند مريضات سرطان الثدي واللواتي يخضعن للعلاج الكيماوي

إعداد

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الدكتور أيمن حسين

الدكتورة عايدة القيسي

قدمت هذه الأطروحة استكمالا لمتطلبات درجة الماجستير في الصحة العامة بكليّة الدراسات العليا في جامعة النجاح الوطنيّة في نابلس، فلسطين.

2009

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الملخص

الهدف العام للدراسة :تهدف هذه ألدراسة إلى تقييم مدى فعالية الأساور الضاغطة كمساعدة للأدوية المضادة للقيء والغثيان في منع القيء والغثيان عند مريضات سرطان الثدي واللواتي يأخذن العلاج الكيماوي

هذه دراسة اكلنيكية تقوم على أساس تقسيم المريضات المشاركات وعددهن 126 مشاركة إلى ثلاث مجموعات كل مجموعة تتكون من 42 مشاركة :المجموعة ألأولي : مشاركات يلبسن الأساور الضاغطة في الأماكن الصحيحة لمدة خمس أيام يقمن خلالها بتعبئة استبيان يشمل المعلومات الاجتماعية ,العمر,الحالة الاجتماعية,المسكن ,التعليم ,الحالة المهنية, كما ويشمل الحالة الصحية ,بالإضافة إلى مدى تعرضها للقي والغثيان في السابق .كما ويشتمل هذا الاستبيان على أسئلة من خلالها نستطيع تقيم الوضع الصحي للمريضة على مدى خمسة أيام من أخذها للعلاج الكيماوي ,بالإضافة إلى الأسئلة التي تقيم نوعية الحياة التي تعيشها المريضة في الخمسة أيام ,كما أن هناك سؤال صريح من خلاله تقوم المشاركة بمدى رضاها عن لبس الأساور الضاغطة وهل تقترح على المريضات الأخريات بلبس مثل هذه الأساور.

هناك المجموعة الثانية: والتي تلبس المشاركات الأساور في أماكن ليست صحية وتقوم بالإجابة على أسئلة الاستبيان لمدة خمس أيام من بدء العلاج أيضا.

أما المجموعة الثالثة :لا تقوم المشاركات بلبس الأساور بل تقوم بالإجابة على الأسئلة أيضا لمدة خمس أيام بدون السؤال الذي يختص مدى الرضي عن لبس الأساور.

جميع المشاركات يأخذن نفس العلاج الكيماوي والأدوية الواقية من القي والغثيان

جميع المشاركات يقمن باختيار المغلف الخاص عشوائيا ودون معرفه بأن هناك ثلاث أنواع من المجموعات. كل مشاركة لها الحرية في الدخول في الدراسة والانسحاب متى تشاء

ألنتائج الناتجة عن الدراسة:

بعد التحليل الإحصائي للبيانات باستخدام برنامج س ب س

لم نجد هناك فروق ذات دلالة إحصائية بين المجموعات في حدوث القيء أو الغثيان في 24 ساعة الأولي من اخذ المشاركات العلاج

كان هناك فروق ذات دلالة إحصائية بالنسبة للمجموعة الأولى)المشاركات يلبسن الأساور الضاغطة في الأماكن الصحيحة (حيث كان هناك انخفاض في معدل الغثيان بعد 24ساعة من أخذهن العلاج الكيماوي بالمقارنة مع المجموعة الثالثة (المشاركات لا يلبسن الأساور الضاغطة)

كما كان هناك دلالة إحصائية على انخفاض شدة الغثيان في الأيام من 5-2عند المجموعة الأولى مقارنة مع المجموعة الثالثة

لم يكن هناك دلالة إحصائية على انخفاض القيء المتأخر بالنسبة للمجموعة الأولى مقارنة مع الثانية والثالثة.

الحاجة إلى أدوية مضادة للقي كان هناك انخفاض في عدد الأدوية عند المجموعة الأولى مقارنة مع الثانية والثالثة

لم يكن هناك فروق ذات دلالة إحصائية بين أي من المجموعات بالنسبة لنوعية الحياة للمريضات خلال الأيام الخمسة للعلاج

ألملخص :نستنتج من النتائج للدراسة إن الأساور الضاغطة لها فعالية في انخفاض القيء الغثيان الذي يحصل بعد 24ساعة من العلاج الكيماوي حيث تستطيع النساء اللواتي يخضعن للعلاج الكيماوي أن يلبسن الأساور في البيت لتخفيض الآثار الجانبية للعلاج وبالتالي تخفيض الأدوية المضادة للقيء والغثيان.