SOUTH BAYLO UNIVERSITY

Effectiveness of Acupuncture on PC6 for the Prevention of Chemotherapy-induced Nausea and Vomiting: A Randomized Controlled Trial

by

Bokching Chau

A RESEARCH PROJECT SUBMITTED

IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE

Doctor of Acupuncture and Oriental Medicine

ANAHEIM, CALIFORNIA

December 2019

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APPROVED BY RESEARCH COMMITTEE

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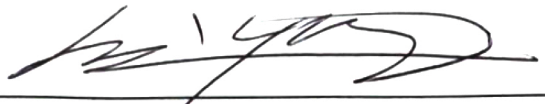

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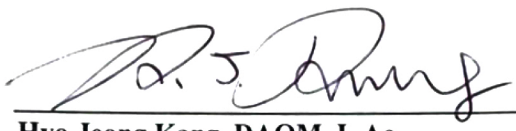

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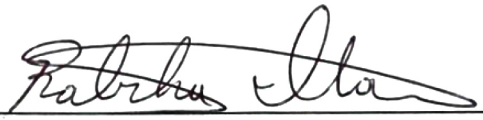

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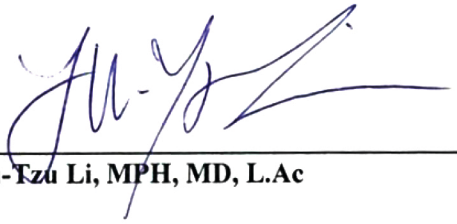

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ACKNOWLEDGEMENTS

I acknowledge South Baylo University in Anaheim, California. I also appreciate the help and efforts from all research staffs.

Effectiveness of PC6 Stimulation for the Prevention of Chemotherapy-induced Nausea and Vomiting: Randomized Controlled Trial

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ABSTRACT

Acupuncture has proven to be beneficial in treating patients with chemotherapy-induced nausea and vomiting (CINV). However, the effects of different acupuncture points, whether it be monotherapy or in combination, remains uncertain in managing CINV. This study aims to use the acupuncture point, PC6 (Pericardium 6), to determine the effectiveness on the prevention of CINV in comparison to PC6 with SP4 (Spleen 4). According to the Traditional Chinese Medicine (TCM) theory, combination therapy of acupuncture points can achieve a synergistic effect. In addition, distal-proximal point association and local distribution point association are standard methods for combining points.

In this non-blinded, randomized controlled trial, I, the acupuncturist, randomly assigned 22 patients with Stage 1 gastrointestinal cancer to receive either standard combination therapy of PC6 and SP4, or PC6 monotherapy. The primary outcome was a composite of duration of nausea and frequency of vomiting.

Over a span of 12 weeks, the drop out rate is 2 of 12 patients (16.7%) in the PC6 monotherapy group and is 2 of 10 patients (20%) in the PC6 and SP4 group (hazard ratio, 0.72; 95% confidence interval (CI), 0.65-0.85; $p<0.05$).

Among chemotherapy patients with Stage 1 gastrointestinal cancer, the nausea duration data from the control group and experimental group shows a significant difference on day 84 (p-value <0.05); While in terms of frequency of vomiting, there is no significant difference among the two groups throughout the research.

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I. INTRODUCTION

With nausea and vomiting as one of the foremost adverse effects of various antineoplastic regimens, there is a crucial need to target the symptoms directly and effectively by using minimal acupuncture points. Chemotherapy-induced nausea and vomiting (CINV) can persist for several days after treatment and can be significantly distressing to the patients' overall quality of life, which may lead to dose reduction or treatment discontinuation, thereby increasing the risk of diseases progression[1]. Although there are effective guidelines on emetogenic chemotherapies for the prevention of CINV, the concern is that it is not widely practiced due to high cost and adverse effects such as headaches, insomnia, dizziness, and constipation[2].

Nausea and vomiting are known as rebellious Qi according to Traditional Chinese Medicine (TCM). A healthy stomach usually has the Qi to push energy downward just like how stomach moves food downward. However, when the stomach is weakened, energy reverses and rises upward leading to symptoms such as nausea, vomiting, and acid reflux. Pericardium 6 (PC6) acupuncture point has been well documented for the treatment of nausea and vomiting[3].

Acupuncture is a type of alternative medicine that is safe with minimal side effects. The evidence of therapeutic effects of acupuncture to manage CINV exists according to the American Society of Clinical Oncology[4]. In light of TCM, it is shown that single acupuncture points and combination acupuncture points can provide similar therapeutic effects depending on the patient's condition[5-9]. However, there is no unanimity that exists

on the optimal point or combination of points for controlling CINV at the time. Therefore, this study aimed to prospectively evaluate the effectiveness of PC6 alone when compared to PC6 with SP4 acupuncture points in the prevention of CINV.

Objectives

The purpose of this study is to determine the effectiveness on the prevention of chemotherapy-induced nausea and vomiting (CINV) between PC6 (Pericardium 6) monotherapy and PC6 with SP4 (Spleen 4) combination therapy. The duration of nausea and frequency of vomiting are evaluated, along with the risk of worsening nausea and vomiting from chemotherapy in patients with Satge 1 gastrointestinal cancer.

Literature Review

According to existing functional magnetic resonance imaging (fMRI) research, acupuncturing the point PC6 can selectively stimulate a hemodynamic response of insula and cerebellar-hypothalamus in order to bring forth the modulatory effects on vestibular functions – hearing, balancing, and spatial orientation[7]. Results showed that acupuncture not only affects brain activity, but also modulates connectivity of the brain which elicit responses in specific regions of the brain, especially pain-related sensory areas.

According to the World Journal of Gastroenterology, Wang and other researchers explored effects of electroacupuncture on the points PC6 alone, SP4 alone, and PC6 and SP4 together[8]. They observed how the points would impact the pathological responses of

the heart and stomach in rats. Results showed no clinically significant difference within the three groups. There was no synergistic action of PC6 and SP4 combined either, indicating that PC6 alone or SP4 alone is just as effective as using the combination in promoting the recovery of cardiac and gastrointestinal activities.

Not only is PC6 famous for nausea and vomiting in general, but has also shown to improve chemotherapy-associated gastrointestinal symptoms in those with gastrointestinal cancer[9]. Gastrointestinal malignancy is not just due to genetics but also diet and high prevalence of Helicobacter pylori, in which populations residing in East Asia have the highest incidence of gastrointestinal cancer. In a recent 2017 study that consisted of 56 patients with gastric cancer, patients would receive 30 minutes of acupuncture therapy daily for 2 weeks, which included PC6 as one of the main points. Researchers concluded that acupuncture has a role in significantly reducing gastrointestinal symptoms induced by chemotherapy and was able to improve the quality of life in patients with advanced gastric cancer. Patients who resorted to using acupuncture to relieve nausea and vomiting showed better outcomes and less side effects from chemotherapy. Common adverse reactions from chemotherapy include but are not limited to gastrointestinal symptoms such as nausea and vomiting, loss of appetite, abdominal pain or bloating, diarrhea, bone marrow suppression, hepatic or renal dysfunction, and allergies.

In another related study, researchers found that stimulating PC6, CV12, ST36, and L14 can effectively prevent CINV[6]. 23 patients receiving highly emetogenic

chemotherapy were given acupuncture sessions throughout their 46 chemotherapy courses, and results showed that all four acupuncture points showed significantly less episodes of vomiting. However, there is no conclusion that researchers came to an agreement on for an optimal acupuncture point in managing CINV. Therefore, this study protocol will expand on previous literature regarding the efficacy of PC6 stimulation on CINV in comparison to the PC6 and SP4 combination.

II. MATERIALS AND METHODS

Recruitment Process

The trial was approved by the Institutional Review Board (IRB) and South Baylo University committee. All participants were recruited from cities in the Los Angeles County. The clinical trial information was advertised in Chinese newspapers on Sing Tao Daily, World Journal, and Chinese LA Daily News. Advertisement was posted weekly from April 2018 to June 2018.

Patients

Participants, both males and females, aged 21 years old and above with a recorded diagnosis of early stage (Stage 1) gastrointestinal cancer and currently receiving chemotherapy were eligible to be selected as cases. Physicians' notes and the participants' pathology reports were to be confirmed with their corresponding doctors. There was also a requirement for life expectancy to be at least one year. They also had to be willing to allocate into one of the two study groups.

Exclusion criteria included diagnosis of terminal stage cancer or hospitalized, or diagnosis of hepatic or renal dysfunction as shown through lab data such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBili) three times upper limit of normal, blood urea nitrogen (BUN) or serum creatinine (SCr) two times upper limit of normal. Other exclusions included active skin infection and nausea and vomiting due to other factors such as opioid medications.

Trial Procedures

In this non-blinded randomized controlled trial, all the patients completed a written informed consent form and entered a 14-day recruitment period in which they were assessed for eligibility and baseline information was gathered. Recruitment period consisted of 2 weeks prior to start of treatment in July. After this recruitment period, participants were randomly assigned to two groups. The positive control group received PC6 and SP4 combination therapy once a week, whereas the experimental group received PC6 monotherapy once a week. The process followed a central randomization in a 1:1 ratio using an interactive web-response system (IWRS). SP4 is located on the medial side of the foot in the depression that is distal and inferior to the base of the first metatarsal bone. PC6 is located three finger width below the wrist on the inner forearm in between the two tendons. In general, the acupuncture treatments in the two groups were based on the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines and recommendations. The STRICTA checklist was followed through to help improve accuracy and reporting of interventions in clinical studies of acupuncture[10]. The checklist comprises of six items: acupuncture rationale, details of needling, treatment regimen, other components of treatment, practitioner background, and control or comparator interventions. Both groups received acupuncture treatments once a week for 12 weeks (12 sessions).

Participants were also monitored for any adverse effects such as swelling, redness, or bruising at the needle insertion site, including any discomfort or dizziness that the patients experienced. These symptoms were recorded in each individual's case report form.

Disposable, stainless steel 1-inch acupuncture needles were used in this trial. The acupuncturist was to insert the needles into the acupuncture points, then stimulate them for Qi sensation to be achieved. Sessions lasted for 35 minutes, with each session scheduled once a week regardless of which days the patients went for their chemotherapy infusion at their own hospital. Interventions occurred according to patients' discretions such as moxibustion and cupping.

Patients were evaluated at 0, 28, 56, and 84 days after randomization, with a focus on assessment of nausea and vomiting, and evaluation of the frequency of nausea and vomiting. Acupuncture was to be discontinued if patients went into remission, became pregnant, or made the decision to stop treatment due to worsening symptoms.

Outcomes

The primary outcome was a composite of duration of nausea and frequency of vomiting. An episode of worsening nausea and vomiting was a need to take their antiemetic medication to the max dose. All treatments and outcomes were performed and adjudicated by me, the acupuncturist with 4 years of experience, who was aware of the trial-group assignments. Worsening nausea and vomiting was evaluated due to the nature of progressive chemotherapy treatments. However, we can see the differences between the two groups under similar conditions.

Statistical Analysis

According to the intention-to-treat principle, I included data from all the patients

who had undergone randomization in the assessments of primary outcomes. Baseline characteristics were evaluated as means or percentages. Time-to-event data were analyzed with the Kaplan-Meier estimator and Mann-Whitney model using the MedCalc statistical software. Kaplan-Meier analysis allowed for estimation comparison of survival over time in the control and experimental groups (Fig. 2)[11]. The Mann-Whitney models were used to calculated hazard ratios, 95% confidence intervals, and p-values[12].

Ethical Review

This project was reviewed and approved by Institutional Review Board of South Baylo University on July 12th, 2018.

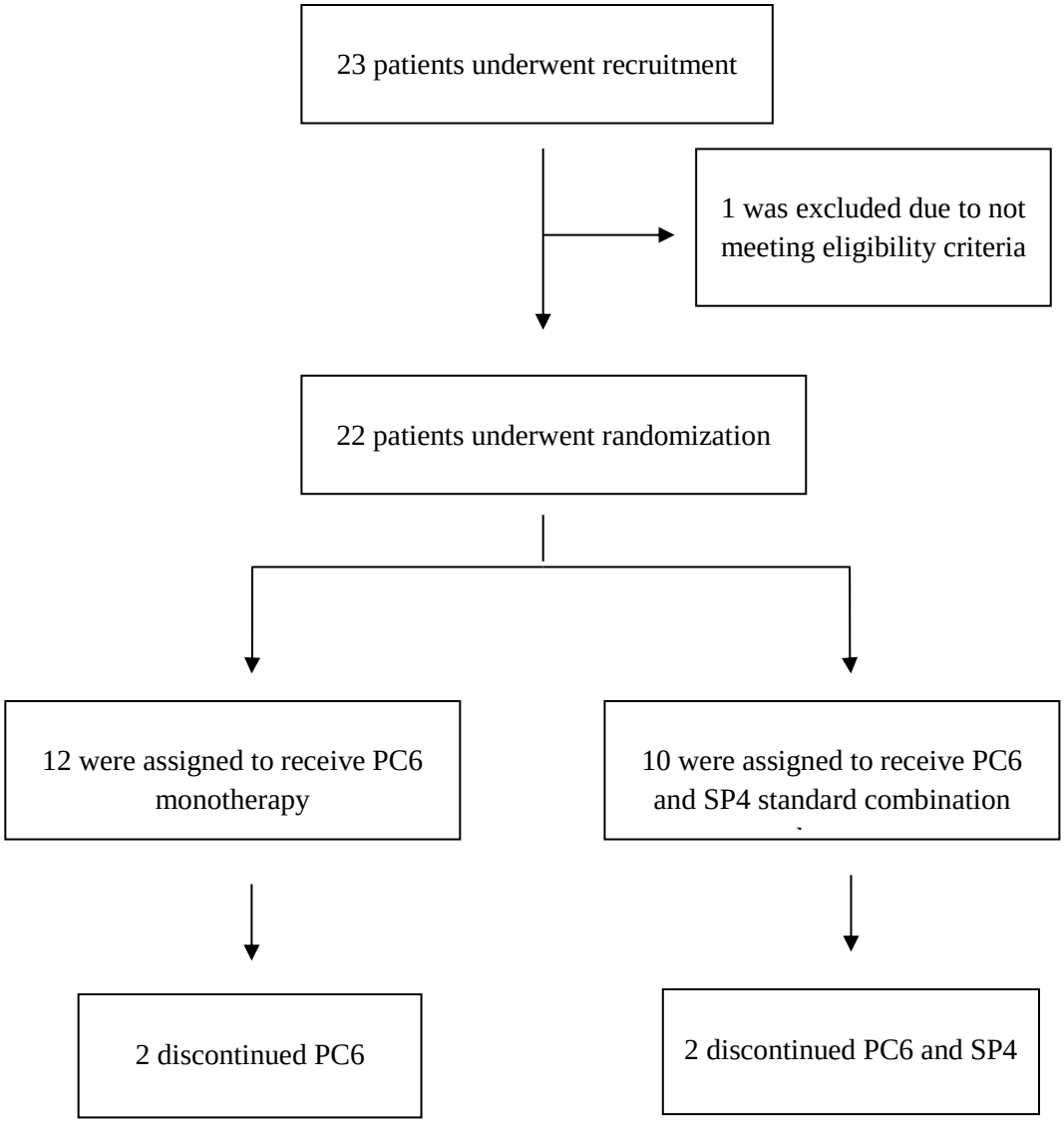

Figure 1. Enrollment and Follow-up. All patients who had undergone randomization were included in the analyses. Patients who discontinued treatment were excluded from the secondary outcome.

Table 1. Patient Characteristics at Baseline.

Characteristic	PC6 and SP4 (n = 10)	PC6 (n = 12)
Sex – n (%)		
Male	7 (70)	10 (83)
Female	3 (30)	2 (17)
Age – years		
Range (SD)	45 – 69 (7.52)	45 – 68 (6.99)
Mean	57	57
Race – n (%)		
Asian	10 (100)	12 (100)
Histologic type – n (%)		
Papillary adenocarcinoma	3 (30)	5 (42)
Tubular adenocarcinoma	2 (20)	2 (17)
Mucinous adenocarcinoma	1 (10)	3 (25)
Signet-ring cell carcinoma	1 (10)	1 (8)
Poorly differentiated carcinoma	3 (30)	1 (8)

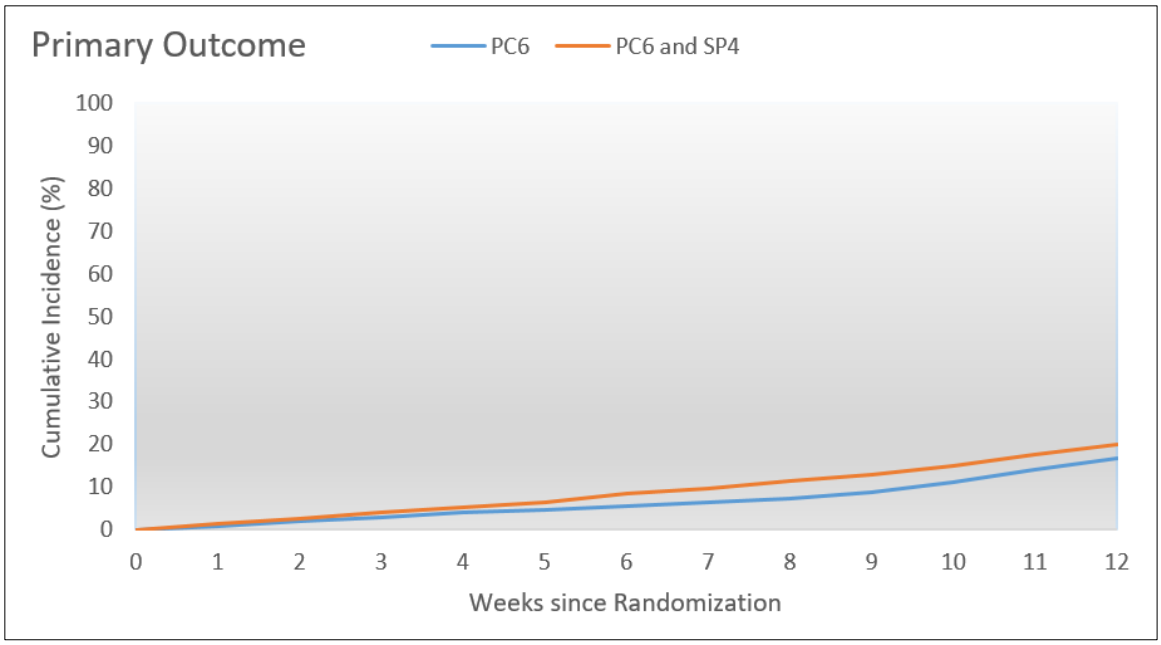

Figure 2. Primary Outcome. The primary outcome was a composite of duration of nausea and frequency of vomiting. The cumulative incidence was estimated using the Kaplan-Meier estimator. This analysis included all the patients who had undergone randomization. The graph shows the follow up period till the end of week 12 (day 84); this is the point at which all patients discontinued treatment.

Table 2. Nausea and Vomiting Symptoms in the control and experimental groups

Characteristic	PC6 and SP4 (n = 10)	PC6[a] (n = 12)	P-Value
Duration of nausea (minutes/day)			
Day 0	11.6±2.57	11.3±2.25	0.8942
Day 24	10.1±5.05	7.8±5.15	0.4939
Day 56	8.2±2.25	5.4±2.28	0.1069
Day 84	7.3±2.25	3±2.15	0.0145
Frequency of vomiting (times/day)			
Day 0	2.6±1.52	2.7±1.50	0.354
Day 24	2.3±1.58	1.6±1.52	0.0725
Day 56	2.2±1.15	1.4±1.15	0.1167
Day 84	2.1±1.23	1.3±1.25	0.0698

[a] P-value < 0.05 for the comparison between the values for the control and experimental groups

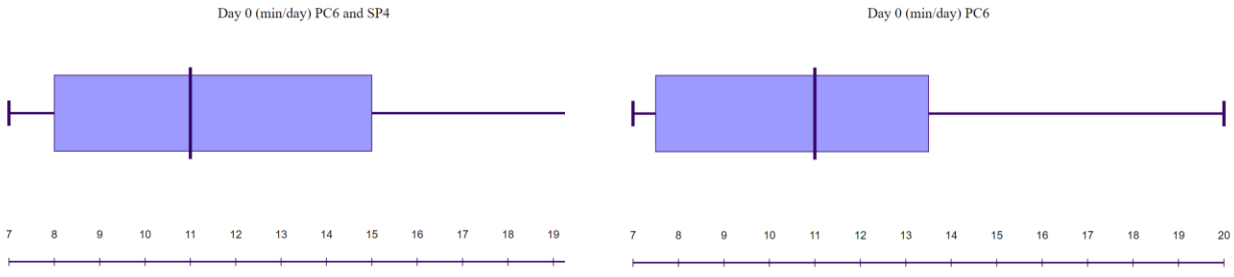

Figure 3. Box and whisker plot for both PC6 and SP4 combination therapy and PC6 monotherapy group at Day 0.

III. RESULTS

From July 2018 through September 2018, a total of 22 patients were randomly assigned to receive either acupuncture points of PC6 and SP4 combination therapy or PC6 alone at Chau Family Acupuncture located in Hacienda Heights, California (Fig. 1). The characteristics for all the patients were well balanced between the control and experimental groups at baseline (Table 1).

Out of 23 participants, 1 of them was excluded from the recruitment process due to not meeting the eligibility criteria of Stage 1 gastrointestinal cancer. Treatment with PC6 was stopped in 2 patients and treatment with PC6 and SP4 was also stopped in 2 patients due to worsening nausea and vomiting (16.7% vs. 20%, $p<0.05$). At the last evaluation, 10 of the patients continued to receive treatment with PC6 (83.3%) and 8 of the patients (80%) continued to receive treatment with PC6 and SP4. The median duration of follow-up was 10.3 weeks (range, 0 to 12).

The primary outcome occurred in 2 of 12 patients (16.7%) in the PC6 monotherapy group and in 2 of 10 patients (20%) in the PC6 and SP4 group (hazard ratio, 0.72; 95% confidence interval (CI), 0.65-0.85; $p<0.05$) (Table 2 and Fig. 2). Event rates for the primary outcome favored PC6 monotherapy. The number of patients who would have needed to be treated with PC6 acupuncture point to prevent one primary event was 30. (95% CI, 15 to 38).

On day 0, the p-value of nausea duration control and experimental group is 0.8942, meaning there is a significant comparability between the two groups. As the research progress, there is a decrease on p-values from day 24, 56 to 84, meaning that the

data significance difference between the two groups are increasing. On day 84, p-values is at 0.0145, it shows that there is a significant difference between the control group and experimental group on day 84 (p-values <0.05). In terms of vomiting frequency, on day 0, the p value between both groups is 0.354. As the research progress, there is a decrease in p-value though day 0, day 24, day 56 and day 84. However despite the lowering values of p-values, thus indicating increasing significance between the two groups, there is no significant difference (p-value<0.05) on day 84. Therefore in terms of vomiting frequency, there is no significant differences between the control group and experimental group.

Throughout the trial period, no infection or bleeding at the acupuncture sites were reported.

IV. DISCUSSION

In this non-blinded, randomized controlled trial involving patients with Stage 1 gastrointestinal cancer and currently undergoing chemotherapy, the composite outcomes of the duration of nausea and frequency of vomiting were lower in the PC6 monotherapy group than in the PC6 and SP4 standard combination therapy group.

The population consisted of all Asians since this trial was advertised in Chinese newspapers only. Most of the patients recruited were already being treated with antiemetics, and only some verbalized their decrease in the use of the medication due to fear of increased risks and side effects from the drug. Therefore, I did not know whether such an effect would have led to the inaccuracy in the treatment of PC6 alone.

This study design minimized bias in several ways. Randomization minimized allocation and selection bias. Its prospective design minimized any recall error and selection bias. Despite patients being aware of the quality measure when assessing the effectiveness and use of PC6 and SP4 acupuncture points, generalizability of the results may have been limited due to selection bias. This would be a result of predictable allocation of participants when the study groups are unmasked. In addition, the small sample size might not have been representative of a general population of patients with gastrointestinal cancers.

In summary, this study concludes that the use of acupuncture point PC6 alone among chemotherapy patients with Stage 1 gastrointestinal cancer was superior to PC6 and

SP4 combination therapy at reducing nausea and vomiting duration per episode end of treatment course; however, the study does not show significant difference on reducing the frequency per day by using the two different methods.

V. CONCLUSION

Before treatment, these two groups are comparable because the p-value is 0.8942 (day 0); therefore, the severity of symptoms are similar. In terms of nausea duration on days 24 and 56, their difference is not significant, which means that both methods show improvement but between the groups there is no clinical significance. However, on day 84, there is a clinical significance between the two groups with a p-value of 0.0145. In terms of the frequency of vomiting before treatment, the results show no significant difference between the two groups with a p-value of >0.05.

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APPENDICES

APPENDIX A

Informed Consent Form

The purpose of this research is to compare the efficacy of acupuncture points PC6, PC6 and SP4, and KD3 on chemotherapy-induced nausea and vomiting (CINV).

This research will be conducted for 21 days starting July in 2018. Individual research subjects will participate in a four day treatment and 15 day follow-up program and subjects will receive different acupuncture points depending on which group they were randomized into. Needles are the sole treatment method utilized for this research and no other treatment methods or tools will be used, with an exception to moxibustion or cupping.

When you consent to participate in this research you will receive acupuncture treatment on day 1 to 5, and follow-up on day 6 to 21 of chemotherapy. From day 6 to 20, you will be asked to log CINV occurrences.

Your participation in this research is entirely voluntary. It is possible that you could experience no benefit from the acupuncture points and you have a right to discontinue your research participation any time you decide to do so. Regardless of your research participation status, you have access to all the services the Chau Family Acupuncture clinic provides.

Any data collected during this research project will be kept confidential to the full extent of the law. A coding system will be used to protect your personal information including your name. All the information will be kept in a confidentially locked cabinet

and only researcher will have access to the information. All the raw data will be destroyed properly once the research is completed.

If you have any question about this study, please contact Bokching Chau at 626-848-3482 or drnathanchau@gmail.com. You may contact Dr. Edwin D Follick, Chair of the South Baylo University Institutional Review Board (IRB) at 714-533-6077 or edfollick@southbaylo.edu for further questions or concerns regarding your rights as a subject in this study.

YOU WILL BE GIVEN A COPY OF THIS FORM WHETHER OR NOT YOU AGREE TO PARTICIPATE.

APPENDIX B

Certificate of Consent

I have read this consent form. The research study has been explained to me, including risks and possible benefits, and other options for treatment. I have had the opportunity to ask questions.

I consent voluntary to participate as a participant in this research.

_____	_____
Name of Participant (print)	Name of Witness (print)
_____	_____
Signature of Participant	Signature of Participant
_____	_____
Date: Day / Month / Year	Date: Day / Month / Year

Statement by the researcher/person taking consent:

I have accurately explained the information sheet to the potential participant. I confirm that the participant was given an opportunity to ask about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been giving freely and voluntary.

A copy of this ICF has been provided to the participant.

_____

Print Name of Researcher / person taking the consent

_____

Signature of researcher / person taking the consent

_____

Date: Day / Month / Year