

Efficacy of acupuncture in prevention of delayed chemotherapy induced nausea and vomiting in gynecologic cancer patients



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HIGHLIGHTS

- Acupuncture is effective in the prevention of chemotherapy-induced nausea and vomiting especially delayed nausea.
- Acupuncture may be used as an alternative treatment option for prevention of chemotherapy-induced nausea and vomiting.

ARTICLE INFO

Article history:

Received 4 August 2014

Accepted 26 October 2014

Available online 31 October 2014

Keywords:

Acupuncture

Chemotherapy induced nausea and vomiting

Gynecologic cancer

Quality of life

ABSTRACT

Objective. To compare the efficacy between acupuncture and ondansetron in the prevention of delayed chemotherapy induced nausea and vomiting (CINV).

Methods. 70 patients were randomized to receive either 1) acupuncture at P6 point before chemotherapy infusion or 2) ondansetron 8 mg intravenously 30 min before chemotherapy infusion in their first cycle with cross-over of antiemetic regimen in the consecutive cycle. All patients received dexamethasone 5 mg orally twice a day for 3 days. Patients were given additional doses of ondansetron 4 mg orally every 12 h if they experienced emesis. Emetic episode, severity of nausea score of 0–10 and adverse events were recorded. Complete response was defined as no nausea, no vomiting and no requirement of additional antiemetic drugs. FACT-G scale was used to evaluate quality of life (QOL) 7 days after each cycle of chemotherapy.

Results. The acupuncture group had a significantly higher rate of complete response in the prevention of delayed CINV (52.8% and 35.7%, $P = 0.02$). Compared to another group, the acupuncture group reported significantly lower delayed nausea (45.7% and 65.7%, $P = 0.004$), nausea score ($P < 0.001$) and fewer dosages of additional oral ondansetron ($P = 0.002$). Adverse effects were also significantly lower in the acupuncture group with less frequent constipation ($P = 0.02$) and insomnia ($P = 0.01$). Overall FACT-G scores were significantly higher in the acupuncture group.

Conclusion. Acupuncture is effective in preventing delayed CINV and in promoting better QOL. With fewer adverse effects, it may be used as an alternative treatment option for CINV.

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Introduction

Chemotherapy induced nausea and vomiting (CINV) is a serious problem in cancer treatment. Up to 80% of patients receiving chemotherapy experience nausea and/or vomiting. CINV reduces quality of life (QOL), induces poor compliance and is a major factor in the discontinuation of treatment [1]. The most common chemotherapy regimen in gynecologic cancer is platinum based chemotherapy with either cisplatin or carboplatin. Both have similar efficacy but cisplatin has higher

emetogenic potential than carboplatin. However, carboplatin is more commonly used in combination with paclitaxel.

There are 5 types of chemotherapy-induced emesis; acute onset, delayed onset, anticipatory, breakthrough and refractory [2]. The two most commonly described types of emesis often causing clinical problems are acute and delayed emesis. Acute onset emesis generally peaks after 5–6 h within the first 24 h of chemotherapy. Delayed onset emesis commonly occurs with platinum administration. It reaches maximal intensity 48–72 h after treatment and can last up to 5 days [2]. Various antiemetic therapies including 5-hydroxytryptamine₃ (5-HT₃) receptor antagonists, neurokinin 1 (NK1) receptor antagonists and dexamethasone have been proven effective in the treatment for CINV [3]. Although these therapies are effective in emetic control, they have been known to cause adverse effects including headache, dizziness, constipation and insomnia [4].

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One traditional Chinese medicine therapy that has been proven safe and effective in the treatment of multiple conditions including CINV is acupuncture. The National Institutes of Health (NIH) Consensus Statement stated that acupuncture is efficacious in preventing chemotherapy-induced emesis with minimal adverse events [5]. Previous meta-analysis studies demonstrated the efficacy of acupuncture in controlling acute CINV, however, no acupuncture trial on delayed CINV exists [6]. Therefore, we aim to study the efficacy of acupuncture compared to 5-HT₃ receptor antagonist (ondansetron) in the prevention of CINV with emphasis on delayed CINV.

Materials and methods

Study design

This study was a randomized trial, crossover study (ClinicalTrials.gov identifier: TCTR20131105001) approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. Randomization was done by block of four using a random number generator. Informed consent was obtained prior to participation of this study.

Study population

Gynecologic cancer patients who were assigned to receive platinum-based chemotherapy (combination of carboplatin and paclitaxel) were enrolled. Patients that were selected for inclusion were patients aged less than 70, with a Karnofsky score of over 80% and those who received first-line chemotherapy treatment. Patients were excluded if they experienced any vomiting or took any antiemetic drugs 24 h prior to treatment, received radiotherapy to the abdominal or pelvic region within 48 h before or the during study, had evidence of brain metastasis, bowel obstruction or any other serious concurrent illnesses.

Study treatments

Chemotherapy

All patients received similar chemotherapy regimens (paclitaxel and carboplatin) according to our standard protocol. Paclitaxel 175 mg/m² was administered intravenously over 3 h followed by carboplatin AUC 5 administered intravenously over 1 h. Thirty minutes before chemotherapy infusion, all patients were given similar premedications including dexamethasone 20 mg, chlorpheniramine 10 mg and ranitidine 50 mg intravenously.

Antiemetic treatments

Patients were randomly allocated to receive one of the following antiemetic treatment regimens.

Treatment A: Manual acupuncture was done on both wrists at P6 point 30 min before and on the following day of chemotherapy administration. The P6 point is located 3 fingers below the flexor crease and between the tendons of the flexor carpi radialis and palmaris longus. A needle was inserted with bilateral rotation and manipulated until patients felt the de Qi sensation and reported soreness, fullness and heaviness. The needle was then left for 30 min. All acupuncture treatments were carried out by the third author (AL) of this study.

Treatment B: A single dose of ondansetron 8 mg was administered intravenously 30 min before chemotherapy.

Patients received either antiemetic regimen A or B for their first cycle of chemotherapy and were crossed over to the other regimen for their consecutive cycle within a three-week period. All patients received oral dexamethasone 5 mg twice a day for 3 days. Additional doses of

ondansetron 4 mg were given orally every 12 h if patients had experienced any nausea and/or vomiting.

Outcome measures

The primary outcome was complete response rate of delayed emetic control, defined as no emesis, no nausea, and no requirement of additional antiemetic drugs. Secondary outcomes included acute emetic control, adverse events and impact of CINV to QOL between both groups. Acute CINV was classified as emesis or nausea occurring within the first 24 h after chemotherapy. Delayed CINV was classified as emesis or nausea which occurs during days 2 to 5 after receiving chemotherapy. Patients were assigned to record emesis episode, severity of nausea, number of additional doses of oral ondansetron and adverse events during the first 5 days. Emesis was defined as vomiting (projection of gastric contents with resultant emesis) or retching (an attempt to vomit but no gastric contents through the mouth). Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Severity of nausea was graded using a numeric scale ranging from 0 (no nausea) to 10 (nausea as bad as it could be) [7]. To assess quality of life after antiemetic treatment, all patients completed the Thai version of Functional Assessment of Cancer Therapy-General (FACT-G) QOL questionnaire version 4.0 at 7 days after receiving each cycle of chemotherapy. This questionnaire consists of 4 subscales; physical, social, emotional, and functional well-being. Scores are calculated so that a higher score indicates better QOL [8]. After the second cycle of treatment, patients were asked to indicate their preferred treatments.

Statistical analysis

Sample size calculations were based on a pilot study of 10 patients. It was assumed that patients who received acupuncture had a complete response rate of 60% in delayed phase but only 40% in patients who received ondansetron. To detect a significant difference between these two treatments with a power of 90% and type I error of 5%, the calculated number of patients was 63. After factoring in a 10% drop out rate, the total sample size required was 70 patients.

Categorical data such as emetic control, adverse events and patient's preferred treatment were analyzed with McNemar Chi-square test. Continuous data such as number of emetic episodes and nausea score were analyzed with Wilcoxon rank sum test. FACT-G score was analyzed with paired *t*-test. A *P* value less than 0.05 was regarded as statistically significant.

Results

Between May 2013 and March 2014, 103 eligible patients were enrolled into the study. Twenty-five patients did not meet the inclusion criteria, 8 declined to participate and the remaining 70 patients were randomized and used for analysis. No subject was lost to follow-up or quit the study (Fig. 1). The mean age of patients was 51.6 ± 9.4 years. The most common type of cancer was ovarian cancer (65.7%), followed by endometrial cancer (17.1%), primary peritoneal cancer (5.7%), two primary cancers (5.7%), fallopian tube cancer (2.9%) and cervical cancer (2.9%).

A comparison of acute and delayed emetic control between acupuncture and ondansetron is shown in Table 1. Similar emetic control for acute CINV was reported in both treatment regimens. However, for prevention of delayed CINV, there was a significantly higher complete response rate in the acupuncture group than in the ondansetron group (52.8% vs 35.7%, *P* = 0.02). Delayed emesis control was comparable in both groups at 74.3% and 70%, respectively. Delayed nausea control was significantly higher in the acupuncture group (54.3%) than in the ondansetron group (34.3%) (*P* = 0.004). Additionally, the acupuncture group had a significantly lower number of emetic episodes and nausea score in delayed onset (*P* = 0.04 and *P* < 0.001, respectively)

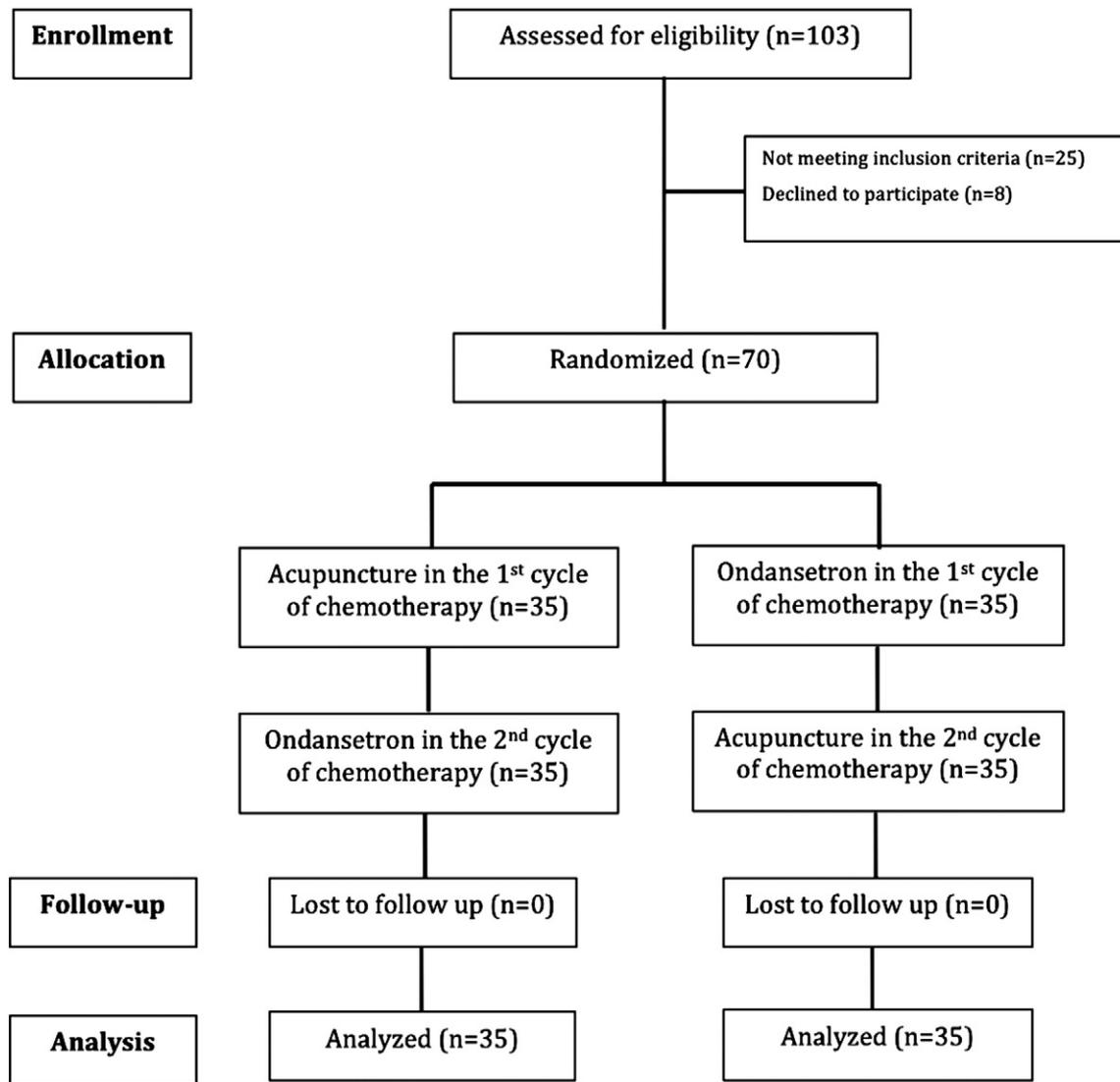


Fig. 1. Flow diagram.

(Table 1). Emetic control according to treatment sequence is detailed in Table 2. Higher complete response for delayed CINV, especially delayed nausea, and lower nausea score were observed in acupuncture group in both treatment sequences. In addition, there was a significantly lower median number of patients requiring additional doses of oral ondansetron in the acupuncture group 0 (0–10) than in the ondansetron group 1 (0–10) ($P = 0.002$).

Adverse events in the acupuncture and ondansetron groups were reported in 42 patients (60%) and 66 patients (94.3%), respectively. Constipation and insomnia were found to be significantly lower in the acupuncture group. (Table 3) However, other adverse events were not significantly different between the two groups. All patients that received acupuncture felt soreness and minimal pain at the acupuncture site. However, these symptoms occurred temporally.

Table 1
Emetic control.

		Acupuncture N = 70	Ondansetron N = 70	P value
Acute emetic control	Complete control	49 (70%)	49 (70%)	1.00
	No emesis	56 (80%)	59 (84.3%)	0.58
	No nausea	52 (74.3%)	50 (71.4%)	0.80
	Emetic episode, median (range)	0 (0–20)	0 (0–6)	0.26
	Nausea score, median (range)	0 (0–9)	0 (0–8)	0.91
Delayed emetic control	Complete control	37 (52.8%)	25 (35.7%)	0.02
	No emesis	52 (74.3%)	49 (70%)	0.55
	No nausea	38 (54.3%)	24 (34.3%)	0.004
	Emetic episode, median (range)	0 (0–4)	0 (0–10)	0.04
	Nausea score, median (range)	0 (0–7)	3 (0–8)	<0.001

Complete control = no emesis, no nausea and no requirement of additional antiemetic drugs.

Table 2

Emetic control according to the treatment sequence.

		Complete control	No emesis	No nausea	Emetic episode median (range)	Nausea score median (range)
Arm A: Acupuncture then ondansetron						
Cycle 1 (n = 35)	Acute	23 (65.7%)	25 (71.4%)*	25 (71.4%)	0 (0–8)	0 (0–8)
	Delay	19 (54.3%)	26 (74.3%)*	19 (54.3%)*	0 (0–4)	0 (0–7)*
Cycle 2 (n = 35)	Acute	27 (77.1%)	32 (91.4%)*	27 (77.1%)	0 (0–3)	0 (0–8)
	Delay	13 (37.1%)	25 (71.4%)*	12 (34.3%)*	0 (0–5)	3 (0–8)*
Arm B: Ondansetron then acupuncture						
Cycle 1 (n = 35)	Acute	22 (62.9%)	27 (77.1%)	23 (65.7%)	0 (0–6)	0 (0–7)
	Delay	12 (34.3%)	24 (68.6%)	12 (34.3%)*	0 (0–10)	3 (0–7)*
Cycle 2 (n = 35)	Acute	26 (74.3%)	31 (88.6%)	27 (77.1%)	0 (0–20)	0 (0–9)
	Delay	18 (51.4%)	26 (74.3%)*	19 (54.3%)*	0 (0–4)	0 (0–5)*

Complete control = no emesis, no vomiting and no requirement of additional antiemetic drugs.

* $P < 0.05$.

FACT-G scores of both groups are shown in Table 4. The acupuncture group had a significantly higher overall FACT-G score compared to the ondansetron group ($P = 0.03$). About 40–45% of patients reported no difference in treatment preference to both treatment sequences. However, an analysis of the 40 patients who reported a treatment preference revealed that there was a significant preference of acupuncture over ondansetron ($P = 0.004$) (Table 5).

Discussion

In this study, we reported comparable efficacy between acupuncture and ondansetron in the prevention of acute CINV. However, acupuncture seemed to be better in the prevention of delayed CINV especially, delayed nausea with less adverse events and better quality of life score than ondansetron.

According to many clinical guidelines for the prevention of CINV in patients receiving moderately emetogenic chemotherapy, a 2-drug combination with a 5-HT₃ receptor antagonist and dexamethasone is recommended [2,9,10]. Intravenous 5-HT₃ receptor antagonist and dexamethasone should be given before chemotherapy for acute emesis control followed by oral 5-HT₃ receptor antagonist or dexamethasone for delayed emesis control. Although 5-HT₃ receptor antagonists are highly effective in preventing acute CINV, they have notably lower efficacy in preventing delayed CINV [3].

Acupuncture, a non-pharmacologic treatment, has been widely accepted for various medical conditions including cancer care [11]. It may be an alternative treatment option for controlling CINV. The mechanism of acupuncture in reducing CINV has not been clearly explained. It may stimulate nerves in muscles, relaying the signal to the spinal cord and brain, which in turn, leads to the release of neurotransmitters and neurohormones. More than 300 acupuncture points are located on the body and each point has its own therapeutic indication. The pericardium 6 (P6 or Neiguan), stomach 36 (ST36), stomach 44 (ST44), and convention vessel 12 (CV12), have been used to reduce nausea and vomiting [12]. However, P6 is the most common acupuncture point for emetic control. P6 can be stimulated by various methods including manual acupuncture (insertion and manual rotation of a very fine needle), electroacupuncture (passing electrical current through the

inserted needle), noninvasive electrostimulation (passing electrical current via electrodes on the skin surface), and acupressure (pressing the point with the fingers or wearing an elastic wristband with an embedded stud) [6].

Efficacy of acupuncture point stimulation has both positive and negative effects on CINV. The meta-analysis of 11 randomized controlled trials (RCT) reported that electroacupuncture plus antiemetic agents showed a significant reduction in acute vomiting. Acupressure was effective for acute nausea but not for acute vomiting. Noninvasive electrostimulation was not effective for any outcomes [6]. However, no evidence of benefits for delayed vomiting and nausea were reported. In addition, acupuncture site stimulations in these studies were noninvasive. No manual acupuncture or electroacupuncture trial evaluated the efficacy on delayed emesis.

There was one RCT which studied manual acupuncture on acute CINV. This study reported no significant difference between acupuncture and control groups in acute CINV [13]. Similar efficacy for controlling acute CINV between acupuncture and standard antiemetic agents was also shown in our study. Up to 70% of patients reported no nausea and no vomiting within the first 24 h in both treatment arms. However, our study differed from the previous study in that acupuncture was not used as an adjunctive treatment with 5-HT₃ receptor antagonist for acute CINV. This result suggests that acupuncture alone might have efficacy on acute emetic control.

Another interesting concern of delayed CINV worth mentioning is its significant impact on QOL. Particularly, the fact that delayed nausea has more impact on QOL than delayed vomiting [14]. The incidence of delayed CINV is much higher than acute CINV. Despite adequate antiemetic treatments, acute vomiting (13.2%) and acute nausea (36.6%) was found in moderately emetogenic chemotherapy. Delayed vomiting and nausea was reported at 27.9% and 52.4%, respectively [14]. These results were comparable to our study where 15.7% of patients experienced acute vomiting and 28.6% experienced acute nausea. Delayed emesis and nausea was 30% and 65.7%, respectively. Acupuncture as an adjunctive treatment with oral dexamethasone revealed the potential benefits for delayed CINV. There were more patients who had

Table 3

Adverse events.

Events	Acupuncture N = 70	Ondansetron N = 70	P value
Headache	5 (7.1%)	6 (8.6%)	1.00
Constipation	19 (27.1%)	31 (44.3%)	0.02
Diarrhea	2 (2.8%)	7 (10%)	0.18
Dyspepsia	8 (11.4%)	7 (10%)	1.00
Sedation	6 (8.6%)	4 (5.7%)	0.62
Insomnia	2 (2.8%)	11 (15.7%)	0.01

Table 4

Quality of life.

FACT-G	Acupuncture N = 70	Ondansetron N = 70	P value
PWB	18.9 ± 5.3	18.0 ± 4.7	0.06
SWB	21.2 ± 4.3	20.6 ± 4.6	0.05
EWB	18.5 ± 3.4	18.3 ± 3.3	0.58
FWB	17.5 ± 4.8	16.9 ± 4.6	0.24
Overall	76.6 ± 12.2	74.0 ± 11.9	0.03

PWB = Physical well-being.

SWB = Social well-being.

EWB = Emotional well-being.

FWB = Functional well-being.

Table 5
Patient's preferred treatment according to the sequence of antiemetic treatment.

Sequence	Preferred acupuncture	Preferred ondansetron	No difference	P value
Acupuncture → Ondansetron (N = 35)	15 (42.9%)	4 (11.4%)	16 (45.7%)	0.67
Ondansetron → Acupuncture (N = 35)	18 (51.4%)	3 (8.6%)	14 (40.0%)	
Total (N = 70)	33 (47.1%)	7 (10.0%)	30 (42.9%)	

*Sub-analysis in 40 patients who reported any preferred treatment; $P = 0.004$.

complete control of delayed CINV, especially delayed nausea after receiving acupuncture. Moreover, the acupuncture group had significantly lower adverse events, especially constipation and insomnia. The lower occurrence of adverse events could be in part due to patients not receiving an ondansetron injection before chemotherapy and perhaps a lesser need of additional rescue ondansetron. However, adverse events might not solely originate from 5-HT₃ receptor antagonists but could possibly be due to other additional agents such as dexamethasone and iron supplementation. As a result, overall FACT-G scores were higher in the acupuncture group. Although, it may not be clinically significant, more patients preferred acupuncture in both treatment sequences.

Our study might be the first RCT with emphasis on manual acupuncture on delayed CINV. The strength of this study was the randomized, cross over trial study design. Outcome measures were compared in the same patient population. Homogeneity of patient population and similar chemotherapy protocol in limited to moderately emetogenic chemotherapy might increase the precision of treatment measurement. Single day chemotherapy infusion with 5 day follow-up was better than a multi-day regimen to differentiate acute CINV from delayed CINV. However, some potential study limitations would indicate that the data was limited to specific populations, gynecologic cancer patients receiving moderately emetogenic chemotherapy, which may not be applicable to other patient populations.

Acupuncture was effective in the prevention of CINV from moderately emetogenic chemotherapy. It still conferred therapeutic success particularly for delayed nausea in many patients with fewer adverse events and better QOL. Acupuncture may be used as an alternative treatment option for CINV prevention especially in patients who are unable to tolerate adverse events of standard antiemetic agents.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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