

# Randomized, Placebo-Controlled Trial of K1 Acupoint Acustimulation to Prevent Cisplatin-Induced or Oxaliplatin-Induced Nausea

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**BACKGROUND:** Greater than 70% of patients with cancer experience chemotherapy-induced nausea and vomiting. In the current study, the authors examined the effects of electrostimulation of the K1 acupoint located on the sole of the foot because it is believed to have the potential to control chemotherapy-induced nausea and vomiting. **METHODS:** In this trial, 103 patients diagnosed with primary or metastatic liver cancer were recruited before transcatheter arterial infusion (TAI) of cisplatin or oxaliplatin and randomized to either group A (51 patients who were treated with the antiemetic tropisetron and acustimulation at the K1 acupoint for 20 minutes approximately 1 to 2 hours before TAI on the first day and then daily for the subsequent 5 days) or group B (52 patients who were treated with tropisetron and electrostimulation at a placebo point on the heel). The rate, intensity, and duration of nausea and vomiting were collected at baseline and then daily for 5 days after TAI. Quality of life was assessed daily using the MD Anderson Symptom Inventory and the EuroQoL scale. **RESULTS:** No differences were found between groups A and B with regard to the incidence and degree of nausea or vomiting on day 1 or the following 5 days. Patients in group A had better EuroQoL scores compared with patients in group B (72.83 in group A vs 65.94 in group B;  $P = .04$ ) on day 4 but not on the other days. No group differences were noted at any time point for MD Anderson Symptom Inventory scores. **CONCLUSIONS:** Electrostimulation of K1 combined with antiemetics did not result in initial prevention of cisplatin-induced or oxaliplatin-induced nausea or vomiting. *Cancer* 2015;121:84-92. © 2014 American Cancer Society.

**KEYWORDS:** cisplatin, oxaliplatin, nausea, vomiting, acupuncture, quality of life..

## INTRODUCTION

Estimates indicate that 70% to 80% of all patients with cancer who are receiving chemotherapy experience nausea and vomiting, symptoms that consistently rank among the top 3 most commonly reported side effects of chemotherapy.<sup>1</sup> Currently, chemotherapy via intraarterial infusions (or transcatheter arterial infusion [TAI]) is the one of the main palliative therapies for patients with advanced liver cancer or those with metastatic disease to the liver, but the side effects of this therapy, such as chemotherapy-induced nausea and vomiting (CINV), negatively affect patients' quality of life (QOL).

The most effective antiemetics used in the management of CINV are type 3 serotonin (5-HT<sub>3</sub>) receptor antagonists,<sup>2,3</sup> including a newer second-generation 5-HT<sub>3</sub> receptor antagonist called palonosetron, as well as corticosteroids and metoclopramide. Another group of antiemetics, the neurokinin-1 (NK1) receptor antagonists, have recently been introduced and, combined with standard therapy, were found to significantly improve the control of emesis in the acute and delayed setting.<sup>4</sup> Unfortunately, these drugs are not effective for all patients and there are potential side effects. Side effects such as headache, transient transaminase elevation, and constipation are common. For some patients, other central

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nervous system effects are possible including extrapyramidal reactions, sedation, and acute dystonic reactions to drugs such as dopamine receptor-blocking agents. The optimal dosing for serotonin antagonists is also controversial and may present a challenge to the effective management of CINV. In addition, to the best of our knowledge, few medications are truly effective at controlling delayed CINV, which occurs >24 hours after infusion.<sup>5</sup> Furthermore, newer drugs such as palonosetron and NK1 receptor antagonists are not easily available for use in many developing countries because they are expensive or not approved for use. Additional strategies for the management of acute and delayed CINV in patients with cancer are therefore clearly needed.

Acupuncture has been practiced in China and other parts of East Asia for thousands of years. It remains a major component of the health care system in Asian communities even today and, according to the World Health Organization, is used in at least 78 countries.<sup>6</sup> Acupuncture can be used to manage various aspects of digestive dysfunction, including nausea, vomiting, constipation, diarrhea, and reflux, as well as postoperative ileus.<sup>7</sup> Acupuncture's mechanisms of action are not well understood, but there is some evidence that its antiemetic effects are partially due to increases in the hypothalamic secretion of beta-endorphins and adrenocorticotrophic hormone with subsequent inhibition of the chemoreceptor trigger zone and vomiting center.<sup>8,9</sup> Acupuncture also regulates the gastrointestinal tract and decreases acid secretion, possibly through both sympathetic and parasympathetic pathways.<sup>8,10,11</sup>

Extensive research has found acupuncture to be useful for the treatment of CINV. In 1998, a National Institutes of Health consensus panel reported that acupuncture was effective in controlling CINV,<sup>12</sup> a finding supported by a more recent systematic review.<sup>13</sup> A placebo-controlled trial also found evidence of the effects of acupuncture in the treatment of patients with CINV when concurrent triple antiemetic pharmacotherapy was used.<sup>14</sup> However, to the best of our knowledge, the majority of research has focused on needle placement in the acupoint pericardium 6 (P6), which may not be convenient or practical in all settings. In addition, a meta-analysis has also examined acustimulation (a practice in which the skin is not broken and electrical impulses are sent through the acupoint using surface electrodes) of P6. The authors concluded that noninvasive electrostimulation of P6 is unlikely to have a clinically relevant impact in patients given state-of-the-art antiemetic drug therapy.<sup>15</sup> However, to our knowledge, clinical trials of electrostimulation

of other acupoints have not been conducted to date. It is possible that electrostimulation of a different acupoint might offer more promising results.

In traditional Chinese medical theory, the meridian (or channel) system is a network of paths through which the life energy known as "qi" flows. Most of the acupoints are situated along the 12 major meridians and interact with their associated internal organs and other related internal structures. The Yongquan (K1) acupoint is the start of the shaoyin kidney meridian of the foot (1 of the 12 regular meridians) and is the point connecting the kidney and heart meridians. Acupuncture of the K1 acupoint has long been used by acupuncturists to treat problems such as insomnia, headache, fever, and dizziness.<sup>16</sup> One study reported that stimulation of K1 successfully treated hiccups<sup>17</sup> and a second study examined pregnancy-induced nausea and vomiting.<sup>18</sup> To our knowledge, the only study to date examining K1 in an oncology setting applied Chinese herbs to K1 acupoint to treat patients with CINV.<sup>19</sup> In this crossover self-controlled study, Chinese herbs (*Evodia rutaecarpa* (Juss.) Benth, *Cinnamomum cassia* Presl, and *Zingiber officinale* Rosc) were applied to the K1 acupoint in 68 patients who received chemotherapy. They found that compared with metoclopramide, herbal treatment at K1 had a higher response rate (89.7% vs 75.0%;  $P<.05$ ) in controlling CINV.<sup>19</sup>

Acustimulation of the K1 point is also believed to potentially help control CINV. The advantage of K1 acustimulation is that it is easy to locate the acupoint and allows for CINV to be controlled using electrostimulation as opposed to having to insert needles. A previous non-randomized trial comparing the effectiveness of ondansetron plus electrostimulation of K1 with ondansetron alone found that patients treated with ondansetron plus electrostimulation experienced a reduced severity of nausea for the first 78 hours after TAI of cisplatin.<sup>20</sup> However, to the best of our knowledge, no randomized controlled trials to date have examined the antiemetic effect of electrostimulating K1. The purpose of the current randomized, single-blind, placebo-controlled study was to examine the effect of K1 acustimulation on controlling both acute and delayed CINV from TAI of cisplatin or oxaliplatin.

## MATERIALS AND METHODS

### Patients

Patients who were scheduled to undergo TAI for primary liver cancer or another primary cancer with liver metastasis were eligible for enrollment in the current trial, which

was conducted at Fudan University Shanghai Cancer Center in Shanghai, China. Additional inclusion criteria were being aged 18 to 75 years and being scheduled to receive TAI using cisplatin or oxaliplatin. Fertile female participants were required to have a negative urine pregnancy test. Exclusion criteria were having received any previous TAI of platinum-based chemotherapy, local skin infections at or near the acupoints, a history of a cerebrovascular or cardiovascular accident or spinal cord injury, nausea and vomiting induced by intestinal obstruction, having vomited or used 5-HT<sub>3</sub> receptor antagonists or other antiemetics within the 24 hours before TAI, having a cardiac pacemaker, currently using acupuncture, and mental incapacity or significant emotional or psychiatric disorders.

### **Procedures**

The study was designed and conceived collaboratively by faculty from both Fudan University Shanghai Cancer Center and The University of Texas MD Anderson Cancer Center (MDACC). The Institutional Review Boards at both centers approved the protocol. Two nurses from Shanghai Cancer Center spent 3 months at MDACC undergoing research nurse training, 2 physicians underwent 2 months of faculty research training, and an acupuncturist from Shanghai Cancer Center spent 1 month at MDACC undergoing research training. During the course of the trial, faculty and staff from MDACC also visited Shanghai Cancer Center 4 times to review the trial. Video conferences were conducted twice each month. Written informed consent, indicating the patient's awareness of the investigational nature of the study, was obtained from all patients.

Patients were recruited before the initiation of chemotherapy, usually 24 hours before TAI. After participants were recruited and had provided informed consent, baseline measures including vital signs, cancer diagnosis and stage, and status of nausea and vomiting within the previous 24 hours were obtained. Patients were then assigned to 1 of 2 groups with the allocation ratio of 1:1 by a form of adaptive randomization, minimization, because this was a small study and simple randomization could result in covariate imbalances.<sup>21</sup> Patient characteristics used to determine group assignment were sex, stage of disease, age, time since diagnosis, type of treatment (cisplatin or oxaliplatin), and primary cancer diagnosis. A nurse who was not participating in the current research study used an adaptive randomization program to ensure proper randomization of the participating patients. This program was created by statisticians at MDACC and was accessed

via a secure MDACC Web site. The acupuncturist was informed by the nurse as to which participants were assigned to the specific group and either the acupuncture points or the sham acupuncture points were marked on the feet of the participants by the acupuncturist or a Chinese medicine physician, but the treatments were delivered by one of the ward nurses. The participants were not aware of the exact location of the acupoints. We further managed to ensure complete blinding of participants by recruiting 1 patient per week (each participant was treated for 6 days and then was discharged from our ward), and avoided the recruitment of patients who shared a room to reduce the opportunity of the patients comparing information with each other. The randomization sequence was kept concealed until the end of the study. Other research nurses who were unaware of group assignments conducted the assessment of the patients. Therefore, participants and the research nurses assessing outcomes were blinded in this study.

### **Treatment**

All patients received tropisetron hydrochloride at a dose of 5 mg with normal saline as an intravenous drip as an antiemetic 30 minutes before TAI. TAI was given only once, with the procedure lasting for approximately 0.5 to 1.5 hours. Patients in group A received bilateral electrostimulation of K1 once daily for 6 consecutive days. Electrostimulation was administered for 30 minutes approximately 1 to 2 hours before TAI on the first day. For the following 5 days after TAI, electrostimulation was administered daily between 7 AM and 9 AM. During treatment, each patient was supine in a hospital bed. The K1 acupoint is located on the sole of the foot in the depression when the foot is in plantar flexion, at the junction of the anterior one-third and the posterior two-thirds of the line connecting the base of the second and third toes with the heel. The acupoints were marked by the acupuncturist in advance, but the stimulation was delivered by a blinded research nurse unaware of the K1 versus sham location. Circular self-adhesive electrodes, measuring 3 cm in diameter, were attached. The acupoint on the left foot was attached with the positive electrode connected to the electrostimulation instrument, whereas that on the right foot was connected to the negative electrode. A continuous wave mode at a frequency of 4 Hertz, with a duration pulse width of 0.15 to 0.3 milliseconds, was used to deliver the electrical stimulation.<sup>20,22</sup> Stimulation intensity was adjusted at a range of approximately 3 to 15 milliampere for 30 minutes at each session based on the highest level the patient could comfortably withstand.<sup>20</sup>

In group B, all procedures were the same as in group A except for the placement of the electrodes, which were attached on the center part of heel, on the sole of the foot on which there are no relevant acupuncture points. The acupoint stimulation equipment used was a G9805-C low-frequency electric pulse treatment device (Shanghai Medical Instrument High-tech Company, Shanghai, China). Ward nurses, who did not have any background in acupuncture or traditional Chinese medicine, were trained on how to apply the electrostimulation. An experienced acupuncturist or Chinese medicine physician marked the bottom of the feet each day as necessary to indicate where on each foot to apply the electrostimulation. Some of the nurses were unaware of the location of the K1 versus the placebo acupoint and as such were blinded to the active versus sham groups. However, this was not consistent across all nurses and as such we cannot claim the trial was a pure double-blind trial.

After TAI, the administration of antiemetics was based on the following criteria. Patients who experienced at least 2 episodes of vomiting within 24 hours or nausea greater than grade 5 of 10 received another dose of tropisetron. If nausea continued to be greater than grade 5 or vomiting continued within 12 hours of tropisetron administration, the patient would receive a third dose of tropisetron. If nausea and vomiting continued after the third dose, the patient would receive dexamethasone. The use of tropisetron and dexamethasone did not differ between the groups.

### Patient Evaluation

Detailed information regarding nausea and vomiting was obtained 24 hours before the first electrostimulation treatment, between the first electrostimulation treatment and TAI, and then daily for 5 days after TAI. Patients were asked to complete daily diaries starting right after the administration of TAI. In the diary, the patient recorded episodes of emesis, the time when each episode occurred, the degree of emesis, and a rating for nausea duration and severity in the previous 24 hours. The intensity of the nausea was rated on a continuous visual analog scale from 0 (no nausea) to 10 (worst possible nausea), which has been validated in previous research.<sup>23</sup> The total duration of nausea was recorded and calculated in minutes. The overall nausea burden was estimated by examining nausea intensity and duration. The degree of vomiting was categorized as very mild, mild, moderate, severe, very severe, or intolerable. All medications taken by the patients were also recorded.

Patients also completed the EuroQoL health state thermometer (scored as 0-100) once every 24 hours. The EuroQoL health state thermometer is a visual analog scale that represents the patient's judgment of his/her own health state, with a higher score indicating a better QOL.<sup>24</sup>

Cancer-related symptoms were assessed using the MD Anderson Symptom Inventory (MDASI), which consists of a core list of symptoms that are common across all cancer diagnoses and treatments as well as modules of additional symptoms that can be included for patients who are receiving aggressive treatment.<sup>25</sup> Patients rated the intensity of physical, affective, and cognitive symptoms on numeric scales from 0 (not present) to 10 (as bad as you can imagine) and this formed the symptom severity index (MDSV). Patients also rated the level of interference that the symptoms had with daily activities and this formed the interference index (MDIN).

### Statistical Analysis

Baseline data of the 2 groups were compared using the Student *t* test for continuous variables and the chi-square test for categorical variables. Our primary analysis focused on whether nausea (score >0) and vomiting (at least 1 episode per day) occurred from the start of TAI through day 6 after TAI. For each of the 2 variables, we compared the proportions of occurrence in each group using the Fisher exact test ( $P < .05$ , 2-sided). Based on an assumption of 50 evaluable patients per group, the study was powered to detect between-group differences of at least 28.5% based on a 2-sided significance level of .05 and 80% power. These calculations are based on the most conservative case, in which 50% of patients experience the symptom in one group compared with 78.5% (or 21.5%) of the patients in the other group.

We also performed analyses of covariance (convarying for baseline score of nausea) in which nausea intensity was treated as a continuous variable. In addition, we examined the difference in the overall number of vomiting episodes (Student *t* test) and the duration of nausea (calculated in minutes and analyzed using the Mann-Whitney *U* test) between the 2 groups.

Secondary analyses based on continuous variables from the MDASI and EuroQoL over all 6 days were performed using a mixed-model analysis of covariance (convarying for baseline score) to determine overall differences in the measurements by group and time and to determine whether there was a significant group-by-time interaction. Analyses were conducted using an "intent-to-treat" model that included all patients.

**TABLE 1.** Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Arm				Chi-Square Test	P
	Group A (n = 51)		Group B (n = 52)			
	No.	%	No.	%		
Sex					0.58	.49
Male	38	74.5	42	80.8		
Female	13	25.5	10	19.2		
Smoking history					0.25	.88
Current smoker	4	7.8	3	5.8		
Former smoker	31	60.8	31	59.6		
Never-smoker	16	31.4	18	34.6		
Alcohol use					0.08	.96
Current	2	3.9	2	3.8		
Former	21	41.2	20	38.5		
None	28	54.9	30	57.7		
Tumor stage					1.08	.78
I	0	0	1	1.9		
II	10	19.6	9	17.3		
III	14	27.5	15	28.8		
IV	27	52.9	27	51.9		
Radiotherapy					0.99	1.00
Yes	0	0	1	1.9		
No	51	100	51	98.1		

This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov). The registration identification number is NCT00430313.

## RESULTS

### Patients

Of the 123 patients who met all initial eligibility criteria, 103 (83.7%) agreed to participate and were randomized to group A (51 patients) or group B (52 patients) from September 2007 to December 2009. The overall mean age of the participants was 53.4 years (range, 20 years-73 years). A total of 23 patients (22.3%) were women and 80 patients (77.7%) were men. A total of 100 patients (97.1%) received oxaliplatin TAI and 3 (2.9%) received cisplatin TAI. Eighty-three patients (80.6%) had advanced cancer (AJCC stage III or IV) and only 1 patient had received radiotherapy. The mean age was  $53.8 \pm 1.5$  years among the patients in group A and  $53.1 \pm 1.6$  years among the patients in group B ( $P = .775$ ). There were no significant differences noted between the groups in terms of demographic or medical characteristics, smoking history, or alcohol use (Table 1).

Four patients in group A (1 patient on day 2, 2 patients on day 3, and 1 patient on day 5) and 4 patients in group B (2 patients on day 3 and 2 patients on day 5) withdrew from the study (Fig. 1).

### Vomiting

There were no significant differences noted between groups with regard to the percentage of patients experiencing episodes of vomiting across the course of the study (29 patients in group A and 23 patients in group B; chi-square, 1.64;  $P = .20$ ) nor did the average number of vomiting episodes differ between groups ( $3.86 \pm 3.56$  in group A and  $4.30 \pm 4.18$  in group B; Student *t* test = 0.41;  $P = .68$ ). Table 2 shows the incidence and degree of vomiting by day for the 2 groups.

### Nausea

There were no significant differences noted between groups with regard to the percentage of patients experiencing nausea for each day of the study. The severity and duration of nausea were also not found to be significantly different between groups (Table 3).

### Secondary Outcomes

Patients in group A reported better EuroQoL scores on day 4 compared with patients in group B (72.83 for group A vs 65.94 for group B;  $P = .037$ ). However, there were no statistically significant group differences noted on the other days (Table 4). There were no group differences noted at any time point for MDASI, MDSV, or MDIN. No adverse events or side effects were found to have occurred in either group.

## DISCUSSION

We found no differences between the groups with regard to the incidence of nausea or vomiting on day 1 or subsequent days, indicating a lack of efficacy of electrostimulation of K1 in preventing acute CINV. Similarly, there were no group differences noted with regard to the median duration of nausea or degree of vomiting on days 2 through 6.

One possible reason that the treatment did not prevent CINV may be that the intervening period between first electrostimulation and chemotherapy was  $>2$  hours for some patients. Patients received K1 electrostimulation at the bedside before they were sent to the operating room for TAI. After the first electrostimulation, the majority of patients waited 1 to 2 hours before receiving the chemotherapy. The effect of acupoint electrostimulation may not last long enough to be observable and may have been weakened for patients who waited too long. It is reasonable to postulate that K1 electrostimulation may not result in enhanced endorphin secretion because if it did, a long treatment response should be apparent. However, to the best of our knowledge, mechanisms of K1



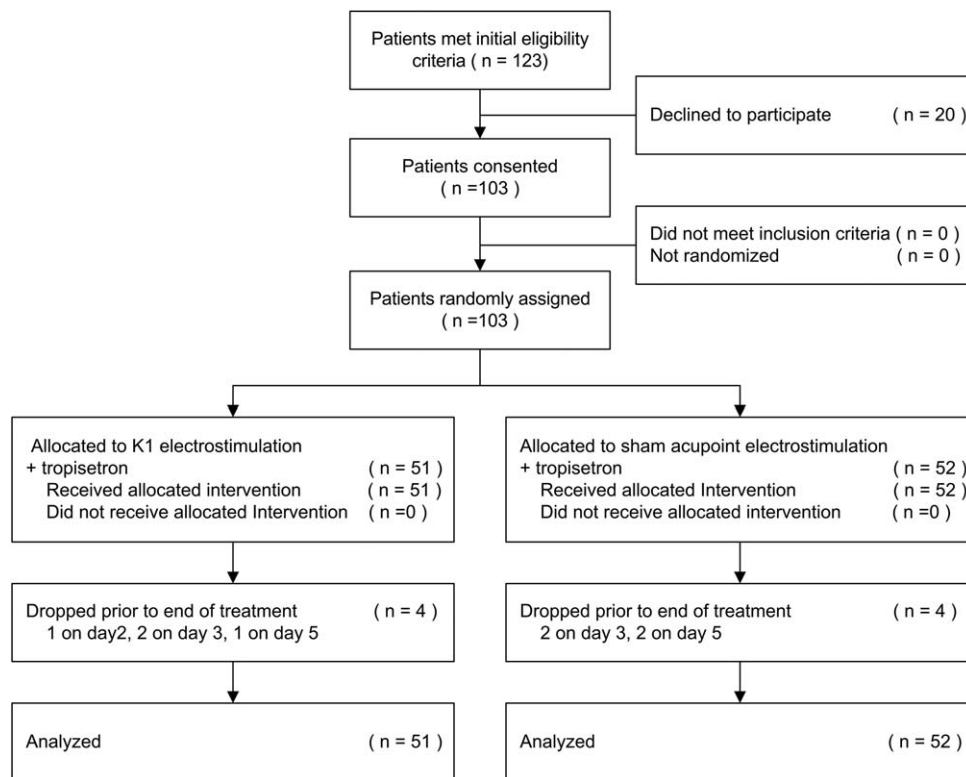


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram is shown.

**TABLE 2.** Comparison Between Experimental and Control Groups in Incidence and Severity of Vomiting Over Time

Day	Group	No. of Patients With Vomiting (%)	Chi-Square Test	P	Degree of Vomiting (%)			Chi-Square Test	P
					No Vomiting	Very Mild to Moderate	Severe to Intolerable		
1	K1 ES	20 (40.0)	3.16	.08	30 (60.0)	15 (30.0)	5 (10.0)	3.41	.18
	Control	12 (23.5)			39 (76.5)	8 (15.7)	4 (7.8)		
2	K1 ES	10 (20.4)	0.12	.73	39 (79.6)	6 (12.2)	4 (8.2)	0.16	.92
	Control	9 (17.6)			42 (82.4)	5 (9.8)	4 (7.8)		
3	K1 ES	8 (17.0)	0.45	.51	39 (83.0)	8 (17.0)	0 (0)	0.45 <sup>a</sup>	.51
	Control	11 (22.4)			38 (77.6)	6 (12.2)	5 (10.2)		
4	K1 ES	9 (19.1)	0.01	.99	38 (80.9)	8 (17.0)	1 (2.1)	4.01	.14
	Control	9 (18.4)			40 (81.6)	4 (8.2)	5 (10.2)		
5	K1 ES	5 (10.6)	<0.001	1.00	42 (89.4)	4 (8.4)	1 (2.1)	<.001 <sup>a</sup>	1.00
	Control	5 (10.6)			42 (89.4)	5 (10.6)	0 (0)		
6	K1 ES	4 (8.9)	0.36	.55	41 (91.1)	3 (6.7)	1 (2.2)	0.96	.62
	Control	6 (12.8)			41 (87.2)	3 (6.4)	3 (6.4)		

Abbreviation: ES, electrostimulation.

<sup>a</sup>The groups with very mild to moderate and severe to intolerable degrees of vomiting were combined.

electrostimulation are not clear and related fundamental research is needed. There were also no group differences noted  $\geq 24$  hours after chemotherapy. However, because the treatments were only given once each day and given that electrostimulation is noninvasive and convenient to apply, increasing its frequency (eg, to 2 or 3 times a day)

may help to achieve better therapeutic effects. Another consideration is that there was weakened polarity between the acupoints. To the best of our knowledge, in the majority of the previous electroacupuncture research, the negative electrode was attached to what is considered the main acupoint, whereas the positive electrode was attached to a

**TABLE 3.** Comparison Between Experimental and Control Groups in Incidence, Severity, and Duration of Nausea Over Time

Day	Group	No. of Patients With Nausea (%)	Chi-Square Test	<i>P</i>	Mean Score of Nausea (SD)	Analysis of covariance	<i>P</i>	Median Duration of Nausea (P25-P75), Minutes	Mann-Whitney <i>U</i> Test	<i>P</i>
1	K1 ES	24 (51.1)	0.51	.48	2.3 (3.0)	0.10	.91	5.0 (0.5-60)	267.5	.87
	Control	21 (43.8)			2.0 (2.8)			4.0 (1-20)		
2	K1 ES	15 (30.6)	0.25	.62	1.5 (2.8)	0.00	.99	5.0 (1-120)	108.5	.34
	Control	18 (35.3)			1.4 (2.5)			3.5 (0.5-30)		
3	K1 ES	19 (40.4)	0.00	.97	1.7 (2.7)	0.01	.94	2.0 (0.5-120)	180.5	.79
	Control	20 (40.8)			1.9 (2.8)			2.8 (0.75-11)		
4	K1 ES	18 (38.3)	0.21	.65	1.7 (2.8)	0.10	.75	2.0 (0.5-5)	158.5	.56
	Control	21 (42.9)			2.0 (2.8)			2.0 (0.5-90)		
5	K1 ES	10 (21.3)	0.90	.34	0.8 (2.0)	0.19	.67	1.0 (0.17-5)	40.0	.15
	Control	14 (29.8)			1.1 (2.0)			3.5 (1-10)		
6	K1 ES	8 (17.8)	0.44	.51	0.7 (2.0)	0.01	.92	1.0 (0.25-3.5)	36.0	.50
	Control	11 (23.4)			0.9 (1.8)			2.0 (1-2)		

Abbreviations: ES, electrostimulation; SD, standard deviation; P25, the 25th percentile; P75, the 75th percentile.

**TABLE 4.** Comparison Between EuroQoL and MDASI Scores Over Time in the Experimental and Control Groups

	Mean EuroQoL (SD)		Analysis of covariance	<i>P</i>	Mean MDASI (SD)		Analysis of covariance	<i>P</i>
	K1 ES	Control			K1 ES	Control		
D 1	63.2 (19.5)	60.5 (17.2)	1.98	.16	29.1 (23.1)	27.8 (20.0)	0.03	.87
D 2	65.0 (17.4)	64.4 (15.1)	0.05	.82	34.9 (21.1)	34.9 (21.6)	0.01	.91
D 3	70.3 (15.6)	69.6 (12.9)	0.02	.89	23.9 (19.5)	24.8 (20.9)	0.11	.74
D 4	73.4 (14.6)	66.3 (18.0)	4.49	.04	21.9 (16.1)	25.6 (19.7)	1.24	.27
D 5	75.1 (15.6)	71.9 (13.3)	0.84	.36	19.9 (14.9)	19.5 (15.5)	0.00	.99
D 6	77.3 (16.7)	76.6 (14.1)	0.08	.78	13.1 (14.0)	16.2 (16.3)	1.71	.19

Abbreviations: ES, electrostimulation; MDASI, MD Anderson Symptom Inventory; SD, standard deviation.

secondary point on the same side of the body to form a current loop, especially for acupoints located on the trunk of the body. However, in the current trial, we were interested in the effect of K1 without the influence of other acupoints based on the effectiveness of the previous non-randomized trial.<sup>20</sup> As such, the K1 acupoint on one foot was stimulated with positive polarity and the K1 acupoint on the other foot was stimulated with negative polarity. This resulted in a larger current loop than using a second acupoint closer to K1 on each side, possibly weakening the stimulation intensity and compromising the therapeutic efficacy.

Another explanation for the null findings of the current study was that the majority of these patients underwent oxaliplatin-based chemotherapy, and only 3 patients underwent cisplatin-based chemotherapy. As an agent with moderate emetogenic potential, oxaliplatin causes a much lower incidence and intensity of CINV and is easier

to manage than cisplatin, which has a high emetogenic potential.<sup>26</sup> Since 5-HT<sub>3</sub> antagonists are the most effective antiemetic drugs for preventing CINV, most patients' symptoms were already well controlled by pharmaceutical antiemetics alone, making it unlikely that acupoint stimulation could dramatically enhance the antiemetic effect of tropisetron. A future trial could consider restricting the study to patients receiving highly emetogenic chemotherapy.

Several systematic reviews<sup>15,27-29</sup> and randomized controlled clinical trials<sup>14,30-33</sup> demonstrated that acupuncture effectively prevents or treats nausea and vomiting from chemotherapy, pregnancy, and surgery. However, traditional acupuncture using needles is not always convenient or possible in many centers. Acupoint electrostimulation is a good alternative because it is safe and easy for nurses or even patients to administer after simple training. A few individual, noninvasive

electrostimulation trials<sup>34-36</sup> have reported some beneficial effects. However, a meta-analysis by Ezzo et al<sup>15</sup> concluded that treatment benefit correlates with the intensity of electrostimulation, with manual and electroacupuncture with the insertion of needles into the skin reported to have better effects than acupressure or surface electrostimulation. Therefore, noninvasive electrostimulation appears unlikely to have a clinically relevant impact when patients are given state-of-the-art antiemetic drug therapy. In the meta-analysis by Ezzo et al, data from 4 original trials were pooled.<sup>15</sup> Acute vomiting was seen in 68 of 308 patients in the noninvasive electrostimulation group (22%) and 78 of 321 individuals in the control group (24%). No protective effects were noted for delayed vomiting or nausea.<sup>15</sup> The majority of research examining the effects of acupuncture on CINV has involved placing a needle in the P6 acupoint and typically includes patients undergoing intravenous-based chemotherapy in an outpatient setting. To the best of our knowledge, the current study is the first randomized controlled trial to evaluate electrostimulation of the K1 acupuncture point plus the use of antiemetics for CINV in individuals undergoing inpatient TAI chemotherapy rather than intravenous chemotherapy. Therefore, these negative findings do not necessarily put into question the results of previous trials.

The results of the current study did find that patients undergoing K1 electrostimulation had significantly better QOL scores on day 4 as well as nonsignificantly higher QOL scores at every other time point. Although it is well known that CINV can impair QOL,<sup>37</sup> to the best of our knowledge few studies of acupuncture among patients with CINV have included QOL assessments. Because the incidence and severity of CINV were similar between the groups in the current study, differences in nausea and vomiting cannot explain the QOL differences noted on day 4. According to recent research, K1 acupuncture stimulation can induce cerebral cortical activation, affecting memory, attention, and self-consciousness as assessed through functional magnetic resonance imaging.<sup>38</sup> Although to our knowledge no systematic research to date has been conducted on K1 stimulation, it is widely used for the treatment of symptoms such as insomnia, headache, fever, buccal ulceration, and dizziness, all of which are common in patients with cancer after chemotherapy and can affect QOL. Although highly speculative, improvements in EuroQoL scores may be related to control of the above symptoms. The improvement in QOL that was noted only on day 4 but not the other days may also be a random observation. Future research should

evaluate the efficacy of K1 electrostimulation for postchemotherapy conditions and its influence on QOL.

One limitation of the current study is that it did not track or formally analyze the use of opioids, which may cause nausea or vomiting; however, through the process of randomization, we believe the effects of opioids were likely to have been similar in both groups. As noted, the frequency of the electrostimulation was only once a day and this may not be sufficient to control CINV. The current study also had several strengths, including the blinded design using a sham acupoint on the heel of the foot close to the real K1 acupoint to ensure that the patients and research nurses who collected the data were blinded to group assignment. The current study also used a homogeneous group of patients who were receiving the same antiemetics before chemotherapy and a standardized antiemetic protocol for CINV.

Electrostimulation of the K1 acupoint combined with antiemetics did not appear to result in the prevention of acute or delayed nausea and vomiting induced by cisplatin or oxaliplatin. However, electrostimulation of K1 combined with antiemetics was found to be more effective than a placebo in transiently improving QOL. Future trials should be considered to focus on patients who have developed CINV after chemotherapy with higher emetic potency with conventional antiemetic regimens. The frequency of electrostimulation and targeting a combination of effective acupuncture points may also increase the efficacy of this noninvasive, easy-to-teach technique.

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## CONFLICT OF INTEREST DISCLOSURES

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