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Randomized, placebo-controlled trial of K1 acupoint acustimulation to prevent cisplatin- or oxaliplatin-induced nausea

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Abstract

Background—More than 70% of cancer patients experience chemotherapy-induced nausea and vomiting (CINV). We examined the effects of electrostimulation of the K1 acupoint located on the sole of the foot, as it is thought to have potential to control CINV.

Methods—In this trial, 103 patients diagnosed with primary or metastatic liver cancer were recruited before trans-catheter arterial infusion (TAI) of cisplatin (CDDP) or oxaliplatin (OXA) and randomized to group A (N=51; treated with the antiemetic tropisetron and acustimulation at the K1 acupoint for 20 minutes, 1-2 hours before TAI on the first day and then daily for the subsequent 5 days) or group B (N=53; 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 (MDASI) and the EuroQoL scale.

Results—No differences were found between groups A and B in the incidence and degree of nausea or vomiting on day 1 or the consecutive 5 days. Patients in group A had better EuroQoL

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This randomized, placebo-controlled trial investigated whether electrostimulation of acupoint K1 could control chemotherapy induced nausea and vomiting. Electrostimulation of acupoint K1 did not result in prevention of acute or delayed cisplatin- or oxaliplatin-induced nausea or vomiting combined with antiemetics in primary or metastatic liver cancer.

scores than did patients in group B (A: 72.83 versus B: 65.94, $P = 0.04$) on day 4 but not on the other days. No group differences were noted at any time point for MDASI scores.

Conclusions—Electrostimulation of K1 combined with antiemetics did not result in initial prevention of CDDP- or OXA-induced nausea or vomiting.

Keywords

cisplatin; oxaliplatin; nausea; vomiting; acupuncture; quality of life

Introduction

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

The most effective antiemetics used in the management of CINV are type 3 serotonin (5-HT₃) receptor antagonists [2,3], including a newer second generation 5-HT₃ receptor antagonist palonosetron (Aloxi), 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, significantly improve emesis control in the acute and delayed setting [4]. 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 nervous system effects are possible including extrapyramidal reactions, sedation, and acute dystonic reactions to drugs such as dopamine receptor-blocking agents. Optimal dosing for serotonin antagonists is also controversial and may present a challenge to effective CINV management. In addition, few medications are truly effective at controlling delayed CINV, which occurs more than 24 hours after infusion [5]. Furthermore, the newer drugs such as palonosetron and NK1 receptor-antagonists not easily available for use in many developing countries due to being expensive or not being for use. Additional strategies for the management of acute and delayed CINV in cancer patients are thus clearly needed.

Acupuncture therapy 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 [6]. Acupuncture can be used to manage various aspects of digestive dysfunction, including nausea, vomiting, constipation, diarrhea, and reflux, as well as postoperative ileus [7]. 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 [8,9]. Acupuncture also regulates the

gastrointestinal tract and decreases acid secretion, possibly through both sympathetic and parasympathetic pathways [8,10,11].

Extensive research has found acupuncture to be useful for treating CINV. In 1998, a National Institutes of Health consensus panel reported acupuncture was effective in controlling CINV [12], a finding supported by a more recent systematic review [13]. A placebo controlled trial also found evidence for the effects of acupuncture at treating CINV, when concurrent triple antiemetic pharmacotherapy was used [14]. Most research, however, has focused on needling 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 point using surface electrodes) of P6. The authors concluded that non-invasive electrostimulation of P6 is unlikely to have a clinically relevant impact in patients given state-of-the-art antiemetic drug therapy [15]. However, clinical trials of electrostimulation of other acupoints have not been conducted. It is possible that stimulation 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 kidney meridian of the foot-shaoyin* (one of the twelve regular meridians) and is the point connecting *the kidney* and *the heart* meridians. Acupuncture of the K1 acupoint has long been used by acupuncturists to treat problems such as insomnia, headache, fever, and dizziness [16]. One study reported that stimulation of K1 successfully treated hiccups [17] and a second study examined the pregnancy-induced nausea and vomiting [18]. The only study examining K1 in an oncology setting applied Chinese herbs to K1 to treat CINV [19]. In this cross-over, self-controlled study, Chinese herbs (*Evodia rutaecarpa* (Juss.) Benth, *Cinnamomum cassia* Presl, and *Zingiber officinale* Rosc) were applied to K1 acupoint in 68 patients who received chemotherapy. They found that compared to metoclopramide, herbal treatment at K1 had a higher response rate (89.7% vs 75.0%, $P < 0.05$) in controlling CINV [19].

Acustimulation of the K1 point is also thought 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 by using electrical stimulation as opposed to having to insert needles. A previous non-randomized trial comparing the effectiveness of ondansetron plus electrical stimulation of K1 with ondansetron alone found that patients given ondansetron plus electrical stimulation experienced reduced severity of nausea for the first 78 hours after TAI of cisplatin (CDDP) [20]. However, no randomized controlled trials have yet examined the antiemetic effect of stimulating K1. The purpose of this randomized, single-blind, placebo-controlled study was to examine the effect of K1 acustimulation on controlling both acute and delayed CINV from TAI of CDDP or oxaliplatin (OXA).

Materials and Methods

Patients

Patients scheduled to undergo TAI for primary liver cancer or another primary cancer with liver metastasis were eligible for enrollment in the trial, which was conducted at Fudan University Shanghai Cancer Center in Shanghai, China. Additional inclusion criteria were being 18 to 75 years old and being scheduled to receive TAI using CDDP or OXA. Fertile female participants had 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 cerebrovascular or cardiovascular accident or spinal cord injury; nausea and vomiting induced by intestinal obstruction; having vomited or used 5-HT₃ receptor antagonists or other antiemetics in the 24 hours before TAI; having a cardiac pacemaker; currently using acupuncture; and mental incapacity or significant emotional or psychiatric disorder.

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. Institutional review boards at both centers approved the protocol. Two nurses from Shanghai Cancer Center spent 3 months at MD Anderson undergoing research nurse training; two physicians underwent 2 months of faculty research training; and an acupuncturist from Shanghai Cancer Center spent 1 month at MD Anderson undergoing research training. During the course of the trial, faculty and staff from MD Anderson also visited Shanghai Cancer Center four 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 this study was obtained from all patients.

Patients were recruited prior to the start of chemotherapy, usually 24 hours before TAI. After participants were recruited and had consented, baseline measures including vital signs, cancer diagnosis and stage, status of nausea and vomiting within 24 hours were obtained. Patients were then assigned to one of two 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 [21]. Patient characteristics used to determine group assignment were sex, stage of disease, age, time since diagnosis, type of treatment (CDDP or OXA), and primary cancer diagnosis. A nurse, not participating in this research study, used an adaptive randomization program to ensure proper randomization of the participating patients. This program was created by MD Anderson statisticians and is accessed via a secure MD Anderson website. 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 doctor, but they did not deliver the treatments as 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 one patient a week (each participant was treated for 6 days and then was discharged from our ward), and avoided recruitment of patients who shared a room

to reduce the opportunity of patients' comparing with each other. The randomization sequence was kept concealed until the end of the study. Other research nurses who were unaware of group assignment conducted the assessment of the patients. Therefore, participants and the research nurses assessing outcomes were blinded in this study.

Treatment

All patients received tropisetron HCl (Saigeen, 5 mg with normal saline, 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 electrical stimulation (ES) of K1 once a day for 6 consecutive days. Electrostimulation was administered for 30 minutes, 1-2 hours before TAI on the first day. For the following 5 days after TAI, electrostimulation was administered daily between 7-9 a.m. During treatment, each patient was supine in a hospital bed. K1 acupoint is located on the sole, of the foot in depression when the foot is in plantar flexion, at the junction of the anterior 1/3 and the posterior 2/3 of the line connecting the base of the 2nd and 3rd 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 K1 versus sham location. Circular self-adhesive electrodes, 3 centimeter in diameter, were attached. Acupoint on left foot was attached with the positive electrode connected to the electro-stimulation instrument, while that on the right foot with the negative electrode. A continuous wave mode at a frequency of 4Hz, 0.15 to 0.3 milliseconds duration pulse width was used to deliver the electrical stimulation [20,22]. Stimulation intensity was adjusted at the range of about 3-15 mA for 30 minutes at each session based on the highest level the patient could comfortably withstand [20].

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 where there are no relevant acupuncture points. The acupoint stimulation equipment used was 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 electrical stimulation. An experienced acupuncturist or Chinese medicine doctor marked the bottom of the feet each day as necessary to indicate where on each foot to apply the stimulation. Some of the nurses were unaware of the location of 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, antiemetic administration was based on the following criteria. Patients who experienced grade 2 nausea or vomiting (at least 2 episodes of vomiting within 24 hours or nausea greater than grade 5 [out of 10]) received another dose of tropisetron. If within 12 hours of tropisetron administration, nausea continued to be greater than grade 5 or vomiting continued, the patient would receive a third dose of tropisetron. If nausea and vomiting continued after the third dose of tropisetron, the patient would receive dexamethasone. The use of tropisetron and dexamethasone did not differ between the groups.

Patient Evaluation

Detailed information about nausea and vomiting was obtained 24 hours before the first ES treatment, between the first ES 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 every emesis occurred, the degree of emesis, a rating for nausea duration and severity for each in the previous 24 hours. The intensity of nausea was rated on a continuous visual analogue scale from 0 (no nausea) to 10 (worst possible nausea) (10 cm), validated in previous research [23]. 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 0-100) once every 24 hours. The EuroQoL health state thermometer is a visual analogue scale that represents the patient's judgment of his/her own health state, with a higher score indicating a better quality of life [24].

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 treatments [25]. 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 two groups were compared by *t* test for continuous variables and chi-square test for categorical variables. Our primary analysis focused on whether nausea (score > 0) and vomiting (at least one episode in a day) occurred from the start of TAI through day 6 post-TAI. For each of the two variables, we compared the proportions of occurrence in each group using Fisher's exact test ($P < 0.05$, two-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 two-sided significance level of 0.05 and 80% power. These calculations are based on the most conservative case, in which 50% of patients experience the symptom in one group compared to 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. We additionally examined the difference of overall number of vomiting episodes (*t* test) and the duration of nausea (calculated by minutes and analyzed by Mann-Whitney U test) between the two 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.

Results

Patients

Of 123 patients who met all initial eligibility criteria, 103 (83.7%) agreed to participate and were randomized to group A (n = 51) or group B (n = 52) from September 2007 to December 2009. The overall mean age of the participants was 53.4 years (range, 20-73years). Twenty-three patients (22.3%) were women and 80 (77.7%) were men. One hundred patients (97.1%) received oxaliplatin TAI and 3 (2.9%) received cisplatin TAI. Eighty-three patients (80.6%) had advanced cancer (stage III or IV) and only one patient had received radiotherapy. The mean age was 53.8 ± 1.5 years in group A, and 53.1 ± 1.6 years in group B ($P=0.775$). There were no differences between groups in terms of demographic or medical characteristics, smoking history, or alcohol use (See Table 1).

Four patients in group A (one patient on day 2, two patients on day 3, and one patient on day 5) and four patients in group B (two patients on day 3 and two patients on day 5) withdrew from the study (See Figure 1).

Vomiting

There were no significant differences between groups in the proportion of patients experiencing episodes of vomiting across the course of the study (group A = 29; group B = 23; $\chi^2 = 1.64$, $P = 0.20$); nor did the average number of vomiting episodes differ between groups (group A = 3.86 ± 3.56 ; group B = 4.30 ± 4.18 ; $t = 0.41$, $P = 0.68$). Table 2 shows the incidence and degree of vomiting by day for the two groups.

Nausea

There were no significant differences between groups in the proportion of patients experiencing nausea for each day of the study. The severity and duration of nausea were also not different between groups (Table 3).

Secondary Outcomes

Patients in group A reported better EuroQoL scores on day 4 than did patients in group B (group A: 72.83; group B: 65.94, $P = 0.037$). However, there were no statistically significant group differences on the other days (Table 4). There were no group differences at any time point for MDASI, MDSV, or MDIN. No adverse events or side effects occurred in either group.

Discussion

We found no differences between groups in 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 in degree and median duration of nausea or degree of vomiting on days 2 through day 6.

One possible reason that the treatment did not prevent CINV may be that the intervening period between first electrostimulation and chemotherapy was more than 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, most 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 stimulation may not result in enhanced endorphin secretion since if it did, a long treatment response should be apparent. However, mechanisms of K1 stimulation are not clear and related fundamental research is needed. There were also no group differences 24 hours or more after chemotherapy. But the treatments were only given one time a day and given that electrostimulation is non-invasive and convenient to apply, increasing its frequency (e.g., twice or three times a day) may help to achieve better therapeutic effects. Another consideration is that there was weakened polarity between the acupoints. In most of the previous electro-acupuncture research, the negative electrode was attached to what is considered the main acupoint, while the positive electrode was attached to a 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 [20]. As such, K1 on one foot was stimulated with positive polarity and K1 on the other foot 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 is that most of our patients underwent OXA-based chemotherapy and only 3 patients underwent CDDP-based chemotherapy. As an agent with moderate emetogenic potential, OXA causes a much lower incidence and intensity of CINV and is easier to manage than CDDP, which has a high emetogenic potential [26]. Although 5HT3 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 to patients getting highly emetogenic chemotherapy.

Several systematic reviews [15,27-29] and randomized controlled clinical trials [30-34] showed 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 as it is safe and easy for nurses or even patients to administer after simple training. A few individual, noninvasive electrostimulation trials [35-37] have reported some beneficial effects. However, a meta-analysis [15] concluded that treatment benefit correlates with intensity of stimulation, with manual and electroacupuncture with insertion of needles into the skin having better effects than acupressure or surface electrostimulation. Therefore, non-invasive electrostimulation seems unlikely to have a clinically relevant impact when patients are given state-of-the-art antiemetic drug therapy. In this meta-analysis, data from four original trials were pooled. Acute vomiting was seen in 68 (22%) of 308 patients in the noninvasive electrostimulation group and 78 (24%) of 321 individuals in the control group. No protective

effects were noted for delayed vomiting or nausea [15]. The majority of research examining the effects of acupuncture on CINV has involved needling the P6 acupoint and typically includes patients undergoing IV-based chemotherapy in an outpatient setting. Our study is the first randomized, controlled trial to evaluate electrostimulation of the K1 acupuncture point plus antiemetics for CINV in inpatients undergoing TAI chemotherapy rather than intravenous chemotherapy. Therefore, these negative findings do not necessarily put into question the results of previous trials.

Our study did find that patients undergoing K1 ES had significantly better QOL scores on day 4 as well as non-significantly higher QOL scores at every other time point. Although it is well-known that CINV can impair quality of life [38], few studies of acupuncture for CINV have included quality of life assessments. As the incidence and severity of CINV were similar between the groups in this study, differences in nausea and vomiting cannot explain the QOL differences 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 [39]. Although there has not been systematic research on K1 stimulation, K1 stimulation is widely used for treating symptoms such as insomnia, headache, fever, buccal ulceration, and dizziness, all of which are common in cancer patients after chemotherapy and can affect QOL. Although highly speculative, improvements in EuroQoL scores may be related to control of the above symptoms. The improvement of QOL 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 post-chemotherapy 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, the authors believe the effects of opioids were likely to have been similar in both groups. As noted, the frequency of the electrostimulation was only one time a day and this may not be sufficient to control CINV. This study also has a number of strengths, including the blinded design using a sham acupoint on the heel of the feet close to the real K1 point to ensure the blinding of patients and the research nurses who collected the data were also blinded to group assignment. The study also used a homogeneous group of patients receiving the same antiemetics before chemotherapy and a standardized antiemetic protocol for CINV.

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

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Figure 1. CONSORT diagram

Table 1

Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Arm		χ^2	P		
	Group A (n = 51)				Group B (n = 52)	
	No.	%			No.	%
Sex					0.58	0.49
Male	38	74.5	42	80.8		
Female	13	25.5	10	19.2		
Smoking history					0.25	0.88
Smoking now	4	7.8	3	5.8		
Used to smoke	31	60.8	31	59.6		
Never smoked	16	31.4	18	34.6		
Alcohol use					0.08	0.96
Drinking now	2	3.9	2	3.8		
Used to drink	21	41.2	20	38.5		
Has never drunk	28	54.9	30	57.7		
Tumor stage						
1	0	0	1	1.9	1.08	0.78
2	10	19.6	9	17.3		
3	14	27.5	15	28.8		
4	27	52.9	27	51.9		
Radiation Therapy					0.99	1.00
Yes	0	0	1	1.9		
No	51	100	51	98.1		

Table 2
Comparison Between Experimental and Control Groups in Incidence and Severity of Vomiting over Time

Day	Group	Number of Patients with Vomiting (%)	χ^2	P	Degree of vomiting (%)			χ^2	P
					No Vomiting	Very Mild to Moderate	Severe to Intolerable		
1	K1 ES	20 (40.0)	3.16	0.08	30 (60.0)	15 (30.0)	5 (10.0)	3.41	0.18
	Control	12 (23.5)			39 (76.5)	8 (15.7)	4 (7.8)		
2	K1 ES	10 (20.4)	0.12	0.73	39 (79.6)	6 (12.2)	4 (8.2)	0.16	0.92
	Control	9 (17.6)			42 (82.4)	5 (9.8)	4 (7.8)		
3	K1 ES	8 (17.0)	0.45	0.51	39 (83.0)	8 (17.0)	0 (0)	0.45*	0.51
	Control	11 (22.4)			38 (77.6)	6 (12.2)	5 (10.2)		
4	K1 ES	9 (19.1)	0.01	0.99	38 (80.9)	8 (17.0)	1 (2.1)	4.01	0.14
	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)	<0.001*	1.00
	Control	5 (10.6)			42 (89.4)	5 (10.6)	0 (0)		
6	K1 ES	4 (8.9)	0.36	0.55	41 (91.1)	3 (6.7)	1 (2.2)	0.96	0.62
	Control	6 (12.8)			41 (87.2)	3 (6.4)	3 (6.4)		

Abbreviations: ES, electrostimulation.

* combined very mild to moderate and severe to intolerable together

Table 3
Comparison Between Experimental and Control Groups in Incidence, Severity, and Duration of Nausea over Time

Day	Group	Number of Patients with Nausea (%)	χ^2	P	Mean Score of Nausea (SD)	F	P	Median Nausea Duration (P25, P75) (minutes)	Mann-Whitney U	P
1	K1 ES	24 (51.1)	0.51	0.48	2.3 (3.0)	0.10	0.91	5.0 (0.5, 60)	267.5	0.87
	Control	21 (43.8)			2.0 (2.8)			4.0 (1, 120)		
2	K1 ES	15 (30.6)	0.25	0.62	1.5 (2.8)	0.00	0.99	5.0 (1,120)	108.5	0.34
	Control	18 (35.3)			1.4 (2.5)			3.5 (0.5,30)		
3	K1 ES	19 (40.4)	0.00	0.97	1.7 (2.7)	0.01	0.94	2.0 (0.5,120)	180.5	0.79
	Control	20 (40.8)			1.9 (2.8)			2.8 (0.75,11)		
4	K1 ES	18 (38.3)	0.21	0.65	1.7 (2.8)	0.10	0.75	2.0 (0.5, 5)	158.5	0.56
	Control	21 (42.9)			2.0 (2.8)			2.0 (0.5, 90)		
5	K1 ES	10 (21.3)	0.90	0.34	0.8 (2.0)	0.19	0.67	1.0 (0.17, 5)	40.0	0.15
	Control	14 (29.8)			1.1 (2.0)			3.5 (1,10)		
6	K1 ES	8 (17.8)	0.44	0.51	0.7 (2.0)	0.01	0.92	1.0 (0.29,3.5)	36.0	0.50
	Control	11 (23.4)			0.9 (1.8)			2.0 (1,2)		

Abbreviations: SD, standard deviation; ES, electrostimulation.

Table 4
Comparison Between Experimental and Control Groups of EuroQoL and MDASI Scores over Time

	Mean EuroQoL (SD)		F	P	Mean MDASI (SD)		F	P
	KI ES	Control			KI ES	Control		
Day 1	63.2 (19.5)	60.5 (17.2)	1.98	0.16	29.1 (23.1)	27.8 (20.0)	0.03	0.87
Day 2	65.0 (17.4)	64.4 (15.1)	0.05	0.82	34.9 (21.1)	34.9 (21.6)	0.01	0.91
Day 3	70.3 (15.6)	69.6 (12.9)	0.02	0.89	23.9 (19.5)	24.8 (20.9)	0.11	0.74
Day 4	73.4 (14.6)	66.3 (18.0)	4.49	0.04	21.9 (16.1)	25.6 (19.7)	1.24	0.27
Day 5	75.1 (15.6)	71.9 (13.3)	0.84	0.36	19.9 (14.9)	19.5 (15.5)	0.00	0.99
Day 6	77.3 (16.7)	76.6 (14.1)	0.08	0.78	13.1 (14.0)	16.2 (16.3)	1.71	0.19

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