Electroacupuncture for Control of Myeloablative Chemotherapy–Induced Emesis

A Randomized Controlled Trial

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Context High-dose chemotherapy poses considerable challenges to emesis management. Although prior studies suggest that acupuncture may reduce nausea and emesis, it is unclear whether such benefit comes from the nonspecific effects of attention and clinician-patient interaction.

Objective To compare the effectiveness of electroacupuncture vs minimal needling and mock electrical stimulation or antiemetic medications alone in controlling emesis among patients undergoing a highly emetogenic chemotherapy regimen.

Design Three-arm, parallel-group, randomized controlled trial conducted from March 1996 to December 1997, with a 5-day study period and a 9-day follow-up.

Setting Oncology center at a university medical center.

Patients One hundred four women (mean age, 46 years) with high-risk breast cancer.

Interventions Patients were randomly assigned to receive low-frequency electroacupuncture at classic antiemetic acupuncture points once daily for 5 days (n=37); minimal needling at control points with mock electrostimulation on the same schedule (n=33); or no adjunct needling (n=34). All patients received concurrent triple antiemetic pharmacotherapy and high-dose chemotherapy (cyclophosphamide, cisplatin, and carmustine).

Main Outcome Measures Total number of emesis episodes occurring during the 5-day study period and the proportion of emesis-free days, compared among the 3 groups.

Results The number of emesis episodes occurring during the 5 days was lower for patients receiving electroacupuncture compared with those receiving minimal needling or pharmacotherapy alone (median number of episodes, 5, 10, and 15, respectively; $P<.001$). The electroacupuncture group had fewer episodes of emesis than the minimal needling group ($P<.001$), whereas the minimal needling group had fewer episodes of emesis than the antiemetic pharmacotherapy alone group ($P=.01$). The differences among groups were not significant during the 9-day follow-up period ($P=.18$).

Conclusions In this study of patients with breast cancer receiving high-dose chemotherapy, adjunct electroacupuncture was more effective in controlling emesis than minimal needling or antiemetic pharmacotherapy alone, although the observed effect had limited duration.

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HIGH-DOSE, MULTIPLE-DAY, multiple-drug myeloablative chemotherapy poses substantial challenges to emesis control. The combination of chemotherapy agents is highly emetogenic; most patients have experienced emesis with multiple courses of prior chemotherapy; and patients may have received other medical care or medications and adjuncts that can contribute to emesis. During the last 2 decades, new effective antiemetic pharmacological agents have helped to improve control of chemotherapy-induced emesis. Because of concerns about pharmacokinetic interaction between high-dose chemotherapy agents and the new antiemetic medications, some patients receiving intense multiple-agent, myeloablative chemotherapy regimens might not be able to use these newer antiemetics concurrently.[1-3] This constellation of factors makes the management of emesis difficult.

A recent National Institutes of Health Consensus Development Conference report concluded that acupuncture was efficacious in reducing emesis associated with chemotherapy.[4] However, it

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was suspected that such benefit was due to a placebo effect. The one published randomized controlled trial that used a sham acupuncture control included 10 patients and was limited by its use of a crossover design without a washout period.[5] Other data that support the use of acupuncture to control emesis include a systematic review and a recent meta-analysis in the postoperative setting.[6,7] However, physiologic reasons suggest that successful treatment with acupuncture might be different between chemotherapy–induced and postoperative emesis.[8,9]

In this study, we assessed a standardized electroacupuncture protocol as an adjunct to antiemetic pharmacotherapy for controlling emesis associated with intensive, multiple-drug, combination myeloablative chemotherapy compared with minimal needling or antiemetic pharmacotherapy alone. We hypothesized a priori that minimal needling treatment might have a greater effect than pharmacotherapy alone because of the nonspecific effects of needles and the additional attention and care the patients received.

METHODS

Study Site and Patients

This study was conducted at a tertiary teaching hospital with a comprehensive cancer center. Patients were recruited from oncology clinics between March 1996 and December 1997 and enrolled successively after written informed consent was obtained. The assessment and intervention procedures were administered when the patients were hospitalized in oncology wards for myeloablative chemotherapy. The study protocol was approved by the local cancer center scientific peer review committee and the institutional human subject protection committee.

Female patients 18 to 62 years of age were eligible if they had histologically proven resected breast cancer, Karnofsky performance status greater than 80 (on 0-100 scale), life expectancy of at least 6 months, and were appropriate candidates for the bone marrow transplantation program. We excluded patients who had brain metastases; life's threatening concurrent nonmalignant conditions; active infection, including an active skin infection over the proposed treatment area; any condition that compromised their ability to give informed consent; or a cardiac pacemaker. A research assistant conducted a face-to-face interview to obtain the following information: sociodemographic characteristics, history of chemotherapy, history of nausea and emesis related to motion sickness, morning sickness, patients' expectations about the adverse effects of chemotherapy, and the benefits of antiemetic treatment.

Randomization Procedure

The patients were randomly assigned without stratification to receive 1 of 3 treatment options: electroacupuncture, minimal needling, or antiemetic drugs alone. The 2 interventions were described to the patient as "classical acupuncture" or "non-classical acupuncture." We used the term *classical acupuncture* to describe a protocol for electroacupuncture at sites that are indicated for nausea and emesis control. We used the term *non-classical acupuncture* to describe a protocol of minimal needling near sites that are not indicated for nausea and emesis control with mock stimulation. Patients were informed that the beneficial effect of either treatment is not known.

Serially numbered, sealed, opaque envelopes were used to indicate assignment. An investigator who had no direct contact with the study patients prepared the envelopes, using a random number table to generate the sequence. Patients were entered into a study log before the envelopes were opened. All envelopes were accounted for.

Treatment Regimens

Chemotherapy. All patients in the 3 groups received the same chemotherapy regimen and antiemetic drugs, following a standard protocol: On hospital days 1, 2, and 3, all patients received high doses of cyclophosphamide and cisplatin, and on day 4, carmustine. Administration of the chemotherapy drugs were as follows: cyclophosphamide, 1875 mg/m^2 body-surface area, per day over 60 minutes, starting at 9 AM for 3 days; cisplatin, 55 mg/m^2 body-surface area, per day with continuous infusion, starting at 9 AM for 3 days; and on day 4, carmustine, 600 mg/m^2 body-surface area, over 2 hours, starting at 9 AM, immediately after the cisplatin dose was completed.

Antiemetic Agents. All patients also received the same triple pharmacological agents for emesis management. The regimen included prochlorperazine prechemotherapy loading, 10 mg in 100 mL of normal saline, intraveneously, over 10 minutes, followed by continuous intravenous infusion at 1 mg/m^2 body-surface area per hour; lorazepam, 1 mg/m^2 body-surface area, intravenously, every 4 hours; and diphenhydramine hydrochloride, 25 mg/m^2 body-surface area, intravenously, every 6 hours. These medications were started 1 hour prior to chemotherapy and were continued until 48 hours after the last chemotherapy infusion. Rescue medications that were available to all patients included additional protocol agent prochlorperazine, lorazepam, and diphenhydramine, as well as metoclopramide and droperidol. Additional medications were given at the discretion of staff physicians not involved in this study as well as at the patient's request.

Electroacupuncture. Patients in the electroacupuncture group received adjunct treatment that consisted of perpendicular insertion of a 36-gauge disposable stainless steel acupuncture needle (Seirin, Japan) at PC6 acupuncture point, located between the tendons of palmaris longus and flexor carpii radialis at 2 body-inches (a body-inch or a *cun* is the greatest width of a patient's thumb at the distal phalanx) above the wrist crease. (This article uses the international nomenclature agreed on by the World Health Organization in 1989[10]). The depth of insertion was 1 body-inch. The needle was inserted with bilateral rotation without introducer and was manipulated until achieving a "de Qi" sensation, that is, the acupuncturist feels sensations from the needle-

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manipulation and the patient feels soreness, fullness, heaviness, or local area distention. The needling technique included twirling, thrusting, lifting, and initial flicking. After de Qi was achieved, the needle was connected through a microalligator clip and an electrode to a battery-operated pulse generator connected to the negative pole. A second needle was inserted perpendicularly to a depth of 1.5 body-inches at the ST36 acupuncture point (located between the tibialis anterior muscle and the tendon of the extensor digitorum longus pedis at 1-finger's breadth lateral to the lower border of tibia tuberosity) with a microalligator clip and an electrode connected to the positive pole. The needling technique included twirling, thrusting, lifting, initial flicking, and periosteal pecking. These procedures were performed bilaterally. This acupunture protocol was based on prior literature, acupuncture textbooks, and suggestions from consultant practitioners following a common symptomatic approach.[11]

Electrical frequency was delivered over 2 to10 Hz, 0.5 to 0.7 milliseconds duration pulse width, under a variable direct current output with square waveform balanced alternating polarity of less than 26 mA for 20 minutes (maximal voltage 15 V). Needling sites were examined at the end of each treatment. Two acupuncture consultants observed the treatment procedure at the start of the study and confirmed the technique.

Two investigators (J.G. and C.C.) administered the procedure in collaboration. One was a clinical instructor at the medical school and had 3 years of acupuncture training; the other was an acupuncture clinician with 20 years of practicing experience. Before the needles were inserted, the clinicians evaluated patients according to traditional pulse diagnosis procedures. The diagnostic ritual was followed daily, although only the standard electroacupuncture protocol was administered. The evaluation and treatment procedure took 30 minutes. The first treatment was scheduled to occur within the 2 hours before the initial chemotherapy infusion, usually between 7 AM and 9 AM on hospital day 1. Treatment was given at the same time over the ensuing days for a total of 5 treatments.

Minimal Needling. For patients in the minimal needling group, a 36-gauge disposable acupuncture needle was inserted subcutaneously with no manipulation or stimulation near the LU7 acupuncture point, located on the lateral aspect of the radius proximal to the styloid process. Care was taken to avoid de Qi sensation. The needle was then connected through a microalligator clip and an electrode to a battery-operated stimulator. A second needle was inserted subcutaneously, with no manipulation or stimulation, near the GB34 acupuncture point, located in the depression anterior and inferior to the head of the fibula, then connected to the stimulator. The needle insertion procedure was performed bilaterally. One acupuncture consultant observed the treatment procedure at the start of the study and confirmed the technique.

This minimal needling protocol was designed by 2 traditional Chinese medical physicians (C.C.). In their opinion, the protocol would not harm patients and, at best, it could improve patients' "lung" and "muscle-skeletal" conditions. However, they thought that the procedure was unlikely to prevent emesis. The stimulator delivered the same audiovisual stimuli as in the electroacupuncture technique for 20 minutes, but *no electrical current* was passed to the needles. Needling sites were examined at the end of each treatment.

Treatment was administered by the same clinicians who administered the electroacupuncture. The diagnostic and treatment ritual was the same as that received by the electroacupuncture group, following the same schedule.

Pharmacotherapy. Patients in the pharmacotherapy alone control group received triple pharmacotherapy agents described above and daily morning visits by physicians and nurses but received no adjunct acupuncture or minimal needling therapy.

Outcome Measures

The primary outcome was the total number of emesis episodes that occurred during the 5-day study period. *Emesis* was defined as projection of gastric contents with resultant emesis product. Severe retching without projection of gastric contents was not considered as an emesis episode. The nurse's recording of the number of daily emesis episodes was used to measure emesis. Nurses were not informed of the treatment group to which a patient was assigned. A count of zero on a study day meant that the patient experienced no emesis. As a secondary outcome, we compared the proportion of emesis-free days across the 3 treatment groups.

For the primary outcome, we summed the daily counts over the 5-day study period. We also instructed patients to record any adverse events that they thought might be attributed to the study. After the 5-day study period, we followed up patients for an additional 9 days, for a total of 2 weeks (14 days).

We abstracted the number of emesis episodes from the nursing records along with strict daily input and output records as measured in milliliters (data not reported here). We also abstracted data from medical charts on the concurrent antiemetic medications administered. Data were collected and entered into electronic files by research assistants who had no knowledge of a patient's treatment group assignment.

Assessment of Blinding

At the end of the 5-day study period, we asked patients who received either type of adjunct needling treatment to complete a questionnaire evaluating various aspects of the procedures. Questions included ratings of the technical quality of the treatment, friendliness of the physician administering the treatment, and the comfort level of the procedure. In addition, we asked patients the treatment group to which they thought they were assigned.

Statistical Analysis

Sample size and power estimation were based on 2-group comparisons of emesis counts, assuming the mean count over the study period was 15 with Poisson distribution (variance equal to the

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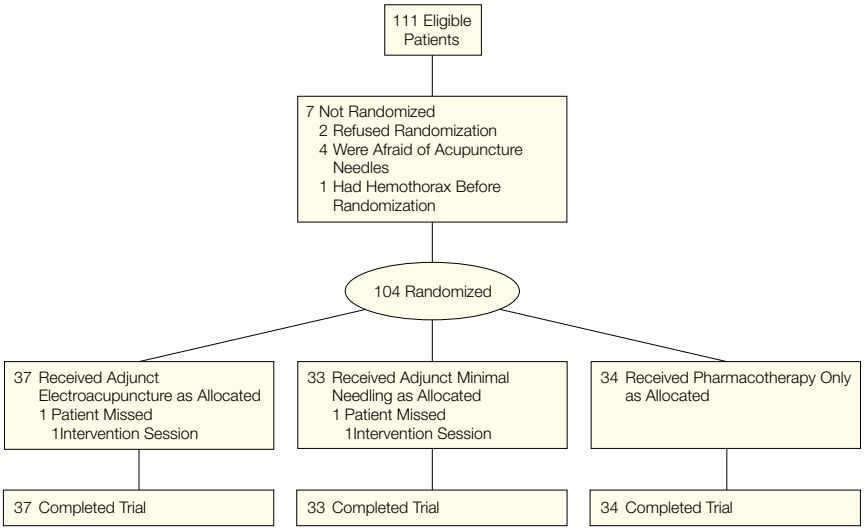
Figure 1. Trial Profile



mean). A design with 35 patients in each of the 3 groups will have 93% and 77% power, respectively, to detect a reduction in the mean emesis count of 25% and 20% with a 2-sided test at the α level of .017 (adjusting for the 3 pairwise comparisons, .05/3). Such effect sizes are conservative estimates based on prior literature.[12,13]

We analyzed data according to the intention-to-treat principal, that is, based on all randomized patients, as randomized. For the primary analysis, the unit of analysis was the patient. We summed the number of emesis episodes over 5 days[14] and analyzed the total as a count variable. Because the primary outcome was not normally distributed and highly variable (ie, some patients had a substantial number of emesis episodes), we analyzed the data using nonparametric tests and quasi-likelihood/Poisson models.

We first compared the nonadjusted outcome among 3 treatment groups using the Kruskal-Wallis test followed by the Wilcoxon rank-sum test for pairwise comparisons. Then, to adjust for a common set of baseline variables predictive of the number of emesis episodes and to take into account the highly skewed distribution of the emesis data, we conducted multivariate analyses using quasi-likelihood/Poisson models.[15] These baseline variables included the patient's age, emesis experience with previous chemotherapy, alcohol use, and experience with anticipatory nausea prior to chemotherapy. The variable selection was based on prior literature[16-18] and achieving a parsimonious model. The Wald test was used to test for differences between treatment groups. For all pairwise comparisons of the 3 treatment groups, we considered a $P=.05$ to indicate statistical significance. According to the Bonferroni adjustment, we used $P<.017$ to adjust for multiple comparison of 3 pairwise comparisons. All P values were 2-tailed.

As a secondary analysis, we compared the proportion of emesis-free days across the 3 treatment groups, adjusting for the same set of baseline variables as in the primary analysis. This analysis was done using a generalized estimating equation (GEE)/logistic model with robust variance estimation.[19] Additional secondary analyses were performed to examine the effect of treatment during the follow-up period; the outcome was the total number of emesis episodes that occurred during the follow-up period, days 6 through 14. First, we used the Kruskal-Wallis test followed by the Wilcoxon rank-sum test to test for differences in the frequency of emesis episodes among groups during the follow-up period. Second, GEE/Poisson models were used to examine whether the effect of treatment on the frequency of emesis episodes was diminished during the follow-up period. We adjusted for the same set of baseline variables in this regression model as we did in the primary analysis. Third, GEE/logistic models were used to examine for a diminished effect, treat the outcomes as either the presence or absence of emesis episodes on a given day, with and without adjusting for the same set of baseline variables.

RESULTS

Patient Recruitment and Follow-up

The recruitment and follow-up of study patients is shown in FIGURE 1. We recruited 111 consecutive eligible patients, of whom 104 were randomized (2 refused randomization; 4 reported a fear of acupuncture needles; and 1 developed hemothorax from a surgical catheter before randomization). Thirty-seven patients were assigned to receive electroacupuncture, 33 to minimal needling, and 34 to pharmacotherapy alone. All but 1 patient received her intended chemotherapy treatments (1 individual received only a partial dose of carmustine due to intolerance) and 2 patients partly deviated from their adjunct minimal needling or electroacupuncture treatment protocol (1 patient was transferred to a cardiac care unit for cardiac toxicity and did not receive all intended intervention sessions; 1 individual missed a treatment session because of a surgical procedure to replace a central catheter).

Two patients experienced adverse effects as a result of the electroacupuncture or minimal needling procedure: 1 patient complained of an electrical shock sensation from the needle-and-stimulator apparatus at the end of the first treatment session and the equipment was immediately removed. The patient reported no complaints on subsequent treatment days. One patient, who had residual peripheral neuropathy manifested as tingling and numbness from prior chemotherapy, complained of an aggravated tingling sensation following each needling procedure.

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Baseline Characteristics

The mean age of participants was 46 years. About two thirds of the patients reported their ethnicity as white and most had a college education (TABLE 1). All patients previously had received chemotherapy, a mean of 6 courses. The vast majority had experienced nausea with prior chemotherapy, and two thirds had experienced emesis associated with previous chemotherapy. More than one fourth reported anticipatory nausea associated with chemotherapy. Patients' baseline characteristics were well matched among groups, except that patients assigned to receive minimal needling had significantly more emesis with prior chemotherapy (difference among groups, $P=.01$).

Assessment of Masking

Most patients reported that they did not know the group to which they were assigned (between patients in the electroacupuncture group and those in the minimal needling group: Pearson $\chi^2_2=4.38$; $P=.11$) (TABLE 2). Patients' ratings of the clinician administering the treatment, the clinician's friendliness, and the technical quality of the treatment they received were comparable across the groups. The majority of the patients gave ratings of excellent, and there were no statistical differences in ratings between those in the electroacupuncture group and those in the minimal needling group. On a 0- to 10-point scale, with 0 being not comfortable at all and 10 being very comfortable, patients in the minimal needling group had a mean rating of 9.1 for comfort of their treatment, compared with a mean rating of 7.8 in the electroacupuncture procedure group (Wilcoxon rank-sum test; $P=.13$).

Other Treatments

All patients received antiemetic medications. Overall, when adjusted to a 24-hour period, a patient received a mean dose of lorazepam, 9.8 mg; diphenhydramine, 103.3 mg; and prochlorperazine, 42.4 mg, per day, including the protocol and rescue doses, during the 5-day study period. The mean amount of triple antiemetic agents administered during the study period was similar across the 3 groups (TABLE 3). During the same period, the use of rescue antiemetics administered in addition to the triple agents also was comparable (Pearson $\chi^2_2=2.23$; $P=.33$; data not shown).

Outcomes

The study outcomes are shown in TABLE 4. Total emesis episodes per person over the 5-day study period differed among the 3 groups (Kruskal-Wallis rank test; $P<.001$) (FIGURE 2). Pairwise comparisons between groups showed that the electroacupuncture group had significantly fewer emesis episodes than the minimal needling group (Wilcoxon rank-sum test; $P<.001$) or the pharmacotherapy alone group (Wilcoxon rank-sum test; $P<.001$), and the minimal needling group had significantly fewer emesis episodes than the pharmacotherapy alone group (Wilcoxon rank-sum test; $P=.01$). Using a quasi-likelihood/Poisson model to adjust for potentially confounding factors, including age, alcohol use, emesis experience with prior chemotherapy, and anticipatory nausea, the differences among groups remained significant. Pairwise comparisons showed that both the minimal needling and electroacupuncture groups had fewer emesis episodes than the pharmacotherapy alone group (β coefficient for electroacupuncture group = −0.36; SE, 0.068; $P<.001$; and β coefficient for minimal needling group = −0.12; SE, 0.063; $P=.02$).

Table 1. Baseline Characteristics of the Participants*

Characteristics	Electroacupuncture Group (n = 37)	Minimal Needling Group (n = 33)	Pharmacotherapy Only Group (n = 34)
Age, mean (SD), y	45.5 (7.4)	43.8 (8.0)	48.0 (6.8)
Self-reported ethnic category, % white (95% CI)	67.6 (52.5-82.7)	63.6 (47.2-80.0)	79.4 (65.8-93.0)
Schooling, mean (SD), y	15.3 (2.5)	14.6 (3.3)	14.6 (2.3)
Prior chemotherapy, %	100	100	100
Emesis with prior chemotherapy, % (95% CI)†	51.3 (35.2-67.4)	84.8 (72.6-97.0)	61.7 (45.4-78.0)
Anticipatory nausea prior to chemotherapy, % (95% CI)	27.0 (12.7-41.3)	27.3 (12.1-42.5)	23.5 (9.2-37.8)
Alcohol use, >5 drinks per week, % (95% CI)	16.2 (4.3-28.1)	21.2 (7.3-35.1)	11.8 (1.0-22.6)

*CI indicates confidence interval.
†Difference among groups, $P = .01$ ($\chi^2_2 = 8.94$, $P = .01$).

Table 2. Assessment of Masking

	Electroacupuncture Group (n = 37)	Minimal Needling Group (n = 33)	χ^2_2	*P* Value
When asked "Which treatment group do you suspect or think you were assigned to?" No. (%)				
Don't know	18 (49)	24 (73)	4.38	.11
Classical*	11 (30)	6 (18)		
Non-classical†	8 (21)	3 (9)		
When asked to rate, % rated excellent (95% CI)‡				
"The quality of acupuncture you received"	62.2 (46.6-77.8)	48.5 (31.4-65.6)	1.32	.25
"The physician acupuncturist that treated you"	75.7 (61.9-89.5)	78.8 (64.9-92.7)	0.10	.76
"The friendliness of the physician acupuncturist"	81.1 (68.5-93.7)	75.8 (61.2-90.4)	0.29	.59

*The term "classical (acupuncture)" was used to describe a protocol for electroacupuncture at sites classically indicated for control of nausea and emesis.
†The term "non-classical (acupuncture)" was used to describe a protocol of minimal needling in sites that are not indicated for control of nausea and emesis with mock stimulation.
‡CI indicates confidence interval. Rating scale: 1, very poor; 2, poor; 3, fair; 4, good; 5, very good; 6, excellent.

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Table 3. Concurrent Antiemetics*

	Daily Mean (SD) Over Days 1-5		
	Electroacupuncture Group (n = 37)	Minimal Needling Group (n = 33)	Pharmacotherapy Only Group (n = 34)
Body-surface area, m^2 (SD)	1.7 (0.16)	1.7 (0.17)	1.7 (0.15)
Lorazepam, mg (SD)	9.2 (2.07)	9.8 (1.67)	10.3 (2.16)
Diphenhydramine, mg (SD)	96.9 (31.63)	105.9 (25.56)	107.2 (29.45)
Prochlorperazine, mg (SD)	42.8 (13.32)	40.7 (12.35)	43.7 (11.31)

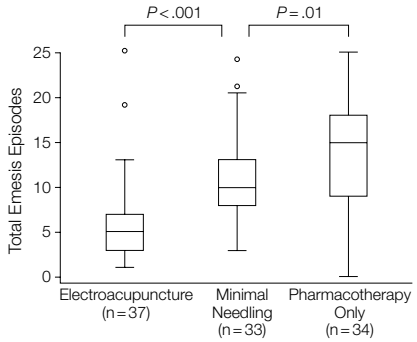
*Dose adjusted to a 24-hour day.

Table 4. Study Outcomes*

	Electroacupuncture Group (n = 37)	Minimal Needling Group (n = 33)	Pharmacotherapy Only Group (n = 34)
Study Period (Days 1-5)			
No. of emesis episodes per person			
Median (range)	5 (1-25)	10 (3-24)	15 (0-25)
Mean (95% CI)†	6.29 (4.20-7.02)	10.73 (7.38-11.90)	13.41 (9.55-15.05)
Percent emesis-free days			
Mean (95% CI)	55 (47-63)	29 (20-37)	20 (11-29)
Follow-up Period (Days 6-14)			
No. of emesis episodes per person			
Median (range)	4 (0-32)	7 (0-30)	8 (0-22)
Mean (95% CI)†	6.89 (3.65-7.34)	8.60 (4.84-9.42)	8.56 (5.29-9.48)
Percent emesis-free days, mean (95% CI)	60 (52-68)	53 (45-62)	52 (44-62)

*CI indicates confidence interval.
†Constructed on square root scale and back transformed to the original scale.

Figure 2. Distribution of the Total Emesis Episodes Per Person During the 5-Day Study Period by Treatment Groups



The lines inside the box represent the median values. The lower and upper borders of the boxes represent the 25th and 75th percentiles. The interquartile range is the height of the box. The whisker lines extend from the box borders to data points that are less than or equal to 1.5 interquartile ranges. Circles outside the whisker lines represent extreme values. *P* values are based on pairwise tests using the Wilcoxon rank-sum test.

Furthermore, the electroacupuncture group had fewer emesis episodes than the minimal needling group (the difference in the β coefficients for electroacupuncture group minus minimal needling group = −0.24; SE, 0.073; $P<.001$).

As a secondary analysis, patients in the electroacupuncture group had a greater proportion of emesis-free days than patients in either the minimal needling group or the pharmacotherapy group (Kruskal-Wallis rank test, $P<.001$). A GEE/logistic model adjusting for the same baseline variables as in the primary analysis showed that the proportion of emesis-free days was significantly greater in the electroacupuncture group compared with either the minimal needling group ($P<.001$) or the pharmacotherapy alone group ($P<.001$). The proportion of emesis-free days was not significantly lower in the minimal needling group as compared with the pharmacotherapy alone group ($P=.18$).

We also used 3 sets of analyses to address the issue of whether the treatment effect from the study period diminished during the follow-up period. Overall, comparing all 3 groups, the sums of emesis episodes as well as the proportion of emesis-free days during days 6 to 14 were not significantly different (Kruskal-Wallis rand test, $P=.18$ and $P=.39$, respectively) We used a GEE/Poisson regression model to test whether the treatment effect was diminished during the follow-up period while adjusting for the same set of baseline variables as in our primary analysis. Results revealed that the difference in emesis counts between the pharmacotherapy and the electroacupuncture groups was diminished in the follow-up period ($P<.001$). All other differences (electroacupuncture group vs minimal needling group and minimal needling group vs pharmacotherapy alone group) were also diminished and were not statistically significant. Similar results were found using the GEE-binary models to treat the outcome as either the presence or absence of an episode on a given day.

In summary, during the follow-up period days 6 to 14, when groups were no longer receiving adjunctive therapy, there were no significant differences among groups in the number of emesis episodes or proportion of emesis-free days.

COMMENT

The results of this study suggest that the addition of daily electroacupuncture treatment to this antiemetic regimen was superior to the pharmacotherapy therapy alone or minimal needling in preventing chemotherapy–induced emesis. There also was a trend indicating that the minimal needling procedure itself was more effective in reducing emesis episodes than pharmacotherapy alone. The observed differences between groups diminished in the follow-up period, which further supported an antiemetic effect of electroacupuncture.

Our study has several strengths and limitations. A principal strength is our use of a minimal needling intervention to assess the potential nonspecific effects of needling and attention and care for the patient. While we could not mask the acupuncturists to the interventions they were delivering, we were able to achieve adequate masking of the patients. This strengthens the internal validity of our study and increases the like-

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lihood that the effect we observed was due to a specific effect of electroacupuncture. A second strength is our use of an electroacupuncture protocol that was standardized, reproducible, and in agreement with the practices of our consultant practitioners, making it more likely that others can attempt to replicate our results. Such attempts at replication are needed as we used only 2 acupuncturists working at a single hospital.

The homogeneity of the patient population and their receipt of a standard protocol for chemotherapy and supportive care increased the precision with which we could measure the treatment effects but limits the generalizability of our findings to other patient populations or those receiving other adjunct therapies. The antiemetic pharmacotherapy used in our study protocol does not include corticosteroids or a serotonin antagonist, such as ondansetron.[20] Use of these agents has been shown to be superior to the agents used in this study for controlling emesis. The effect of electroacupuncture as an adjunct to other antiemetic regimens, including serotonin antagonists and corticosteriods, is unknown.

It is important to note that minimal needling led to a reduction in the frequency of emesis episodes. Attention and the clinician-patient interaction are possible explanations for the beneficial effect in this setting. This finding supports a role for behavioral interventions concomitant to pharmacological management and also suggests that, in future studies evaluating the efficacy of acupuncture, a convincing control and successful masking are critical.

Our study showed that adding a daily electroacupuncture procedure to pharmacotherapy was more effective than pharmacotherapy alone in preventing chemotherapy–induced emesis. Similar results recently have been observed in an animal model.[21] Are there biologically plausible explanations for the observed effect? Pharmacological therapies to manage chemotherapy–induced emesis have been directed at the neurotransmitter receptors in the brain regions receptive to emetic stimuli.[22,23] In a multiple-day, multiple-drug combination chemotherapy setting, emetic responses are aggravated by the multiple agents, their converted products, altered metabolism, and products of cell damage. The complex, multifactorial and severe nature of such chemotherapy–induced emesis suggests that no single antiemetic agent targeting a particular mechanism can be expected to control vomiting completely. Electroacupuncture (repeated sensory stimulation) has been thought to modulate serotonin, substance P, and endogenous opiates along various pathways in the central nervous system.[24-27] We speculate that some of the effects we observed may be manifested through the serotonin- and substance P–mediated components of the emetic reflex, as well as through the opiate μ receptor via its antiemetic actions.[28-30] Future neurophysiological and neurochemical investigations may help us to further understand the complexity of emesis and to broaden the current approach to the spectrum of antiemetic care.

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