A Randomized Controlled Trial of Nerve Stimulation for Relief of Nausea and Vomiting in Pregnancy

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OBJECTIVE: To evaluate the effectiveness of low-level nerve stimulation therapy over the volar aspect of the wrist at the P6 point to treat nausea and vomiting in early pregnancy.

METHODS: Pregnant volunteers ($n = 230$) with symptoms of mild to severe nausea and vomiting between 6 and 12 weeks' gestation participated in a 21-day clinical trial. Participants were randomly assigned to receive a device for nerve stimulation therapy or an otherwise identical but nonstimulating placebo device. The primary outcome measure was self-recorded symptoms according to the Rhodes Index of Nausea, Vomiting, and Retching (Rhodes Index). Secondary outcome measures were medication use, weight gain, and presence of urinary ketones.

RESULTS: Baseline characteristics were similar in both groups. A total of 187 women (81%) completed the trial. Pretreatment Rhodes Index scores for the entire population demonstrated no significant differences between study and control groups. The time-averaged change in Rhodes Index total experience of 6.48 for the study group was significantly better than the control value of 4.65 ($P = .02$). Study patients gained more weight than controls (2.9 versus 1.2 lb, $P = .003$). There were no statistically significant differences in medication use or urinary ketone measurements.

CONCLUSION: Nerve stimulation therapy is effective in reducing nausea and vomiting and promoting weight gain in symptomatic women in the first trimester of pregnancy. (Obstet Gynecol 2003;102:129–35. © 2003 by The American College of Obstetricians and Gynecologists.)

Nausea and vomiting are prevalent symptoms during pregnancy, affecting approximately 70% of women,[1] with one quarter of these women missing work as a result of their symptoms.[2] O'Brien and Naber[3] found that nausea and vomiting can impose substantial lifestyle limitations on pregnant women that can impact both them and their families. Many pharmacologic interventions have been shown to be more effective than placebo in reducing nausea and vomiting in randomized, prospective, clinical trials.[4] However, most women experience their worst symptoms in the first trimester, during embryogenesis, and are often averse to taking any medication for fear of causing birth defects. Also, medications that are effective in relieving nausea and vomiting cause symptoms of sleepiness twice as often as does placebo,[4] and sleepiness can interfere with a woman's ability to work and her other activities of daily living. For these reasons, effective alternative therapies for nausea and vomiting of pregnancy are desirable.

Acupuncture and related techniques have potential for nonpharmacologic relief of nausea and vomiting during pregnancy. The most studied mechanism of stimulation of acupuncture points outside of pregnancy employs penetration of the skin by thin, solid, metallic needles, which are manipulated manually or by electrical stimulation. However, because symptoms of nausea and vomiting during pregnancy may occur throughout the day and generally persist for weeks, alternative forms of acupuncture may be better suited for treatment of this illness.

Stimulation of the median nerve at the P6 or Neiguan acupuncture point by applying pressure at a site on the underside of the wrist (acupressure) has been studied for this purpose. Reports of the effectiveness of this technique from various trials have been contradictory. Dundee et al[5] found pressure at P6 to be effective in reducing severe nausea and vomiting but not effective for occasional to daily nausea. Conversely, Belluomini et al[6] found acupressure to be effective in reducing nausea but that it had no effect on vomiting. De Aloysio and Panacchioni[7] found a greater "positive effect" with acupressure than with placebo. Hyde[8] found that acupressure reduced nausea compared with control in a small group of subjects, whereas in a randomized, placebo-controlled trial, O'Brien et al[9] found that acupressure

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was no more effective than placebo in a large group of subjects. A systematic review of randomized controlled trials (RCTs) concluded that P6 acupressure has beneficial effects. However, the O'Brien trial, which was the largest RCT, with a 92.5% completion rate for study subjects, was excluded from the analysis because of methodologic considerations.[5] A recent RCT of acupuncture to control nausea and vomiting in pregnancy did not demonstrate that treatment was more effective than a sham procedure.[10]

Noninvasive electrical stimulation (acustimulation) of the median nerve at the P6 point has shown promise as an alternative technique to relieve nausea and vomiting secondary to motion sickness,[11] chemotherapy,[12] and postoperative effects of anesthesia.[13] Evans et al[14] conducted a small, randomized, crossover trial of 23 women, which suggested that acustimulation may be more effective than placebo in suppressing pregnancy-induced nausea and vomiting. The purpose of the current investigation was to assess in a rigorous manner whether acustimulation is effective in relieving nausea and vomiting during the first trimester of pregnancy.

MATERIALS AND METHODS

A multicenter, randomized, placebo-controlled trial was developed involving four clinical centers with diverse patient populations. Patients were enrolled from hospital clinics and from physicians' private offices at Morristown Memorial Hospital (Morristown, New Jersey), Eastern Virginia Medical School (Norfolk, Virginia), The University of Arizona Health Sciences Center (Tuscon, Arizona), and The New York University School of Medicine (New York, New York). The hypothesis tested was that nerve stimulation therapy at the P6 acupuncture point on the volar aspect of the wrist would reduce the incidence and severity of nausea and vomiting in the first trimester of pregnancy. The institutional review boards of each center approved the protocol.

Nerve stimulation therapy was accomplished with the ReliefBand Model WB-R (Woodside Biomedical Inc., Carlsbad, CA), which was cleared by the U.S. Food and Drug Administration for use in the treatment of nausea and vomiting in pregnancy. The ReliefBand device is a noninvasive, portable (34 g), battery-powered, watch-like acustimulation device. The skin contact surface has two metal electrodes, through which nerve stimulation therapy is applied. After a hypoallergenic conductive gel is applied to the volar aspect of the wrist, the device is attached to the wrist by a Velcro strap. A rotary dial on the device allows users to select between five intensity levels.

Patients were eligible for the study if they had been experiencing nausea and vomiting for a minimum of 3 days and had an estimated gestational age of between 6 and 12 weeks. In addition, patients were required to be at least 18 years old and have a telephone. Exclusion criteria included the following: conditions other than pregnancy associated with symptoms of nausea and vomiting, including thyroid disease, liver disease, acquired immune deficiency syndrome, diabetes, gall bladder disease, peptic ulcer disease, malignancy treated with chemotherapy, antibiotic therapy, antidepressant medication, alcoholism, or drug addiction. Patients with a cardiac pacemaker were excluded, as were those who had been treated with acupuncture previously.

Once a patient qualified for the study, she was randomized to receive an active device or a sham device that appeared identical to the study device but did not emit an electrical current to the volar aspect of the wrist. Randomization was performed according to a computer-generated list by means of sequentially numbered, opaque, sealed envelopes at each clinical site. Written, informed consent was obtained from each woman before randomization.

Subjects enrolled into the trial underwent a pretreatment examination with a nurse clinician, who performed group assignment by picking the next numbered envelope. Antiemetic medication usage at entry into the trial was recorded. The Rhodes Index of Nausea, Vomiting, and Retching (Rhodes Index)[15] was administered to assess initial symptom severity. This self-report form has eight questions, each answered with a 5-point Likert-type scale that measures the patient's perceived duration, frequency, and distress from nausea, vomiting, and retching. Rhodes Index questions are summarized as continuous scores based on a predefined scoring algorithm. The scoring algorithm assigns a numeric score to each response, and scores are tallied into three subscales summarizing symptom occurrence, distress, and total experience, which combines the occurrence and distress scores. The first subscale summarizes the number of nausea, vomiting, and retching episodes into a "total occurrence score" that ranges from 0 to 20. The second subscale assesses the patient's perceived distress from nausea, vomiting, and retching into a "total distress score" that ranges from 0 to 12. The total distress and occurrence scores are summed to form the "total experience score" which can range from 0 to 32. Patient height, weight, blood pressure, presence or absence of urinary ketones, and specific gravity were also recorded.

Women were instructed in proper usage of the device during the initial visit. To preserve patient blinding, all patients were told that they may or may not feel a "tingling" sensation from the device. Because of the

subjects' different responses to active and sham devices, it was not possible to blind study personnel as to group assignment. Additional research personnel, including those assessing outcomes, were not blinded to group assignment. Patients were told that they could adjust the intensity of the device by rotating a dial to achieve maximum relief from their symptoms.

Patients were given a package of reporting forms and instructed to complete questionnaires for a total of 12 days (days 1–7, 9, 11, 13, 17, and 21) of the 21-day trial. They were asked to complete the Rhodes Index survey twice daily, in the morning and evening, on the assigned days. In addition, they recorded device location (left or right wrist), intensity settings, amount of time the device was worn, and any medications taken. The use of over-the-counter and prescribed medications for nausea was not controlled during the study period. Research personnel telephoned the patient on evaluation days at a time mutually agreed upon between the investigator and the patient to remind her to record the required information from that day. Unanticipated adverse events observed by the investigator or reported by the subjects were recorded on a separate case report form distributed to subjects with the initial package. Patients were provided with stamped, addressed envelopes to return each day's material. An exit interview was scheduled on day 21 of the trial, at which time weight, urinary assessment, and repeat interview was performed.

The primary study outcome was assessment of nausea and vomiting by the Rhodes Index score. Secondary outcome variables were weight gain or loss over the study period, change in urinary ketones and specific gravity, and medication use. Sample size calculations were made with the technique of Liang and Zeger[16] for the estimation of time-averaged differences in a continuous response between two groups. The type I error rate was set at 0.05, power assumed to be 80%, and the number of repeated observations was fixed at 24 (2 per day times 12 days). The smallest meaningful difference was expressed in terms of the measurement standard deviation (delta). Delta was varied from 20% of a standard deviation to 1 standard deviation, and the correlation among repeated observations was varied from 0.3 to 0.9. For all scenarios tested, the proposed sample size, $n = 90$ per group, was adequate to provide 80% power for the detection of at least a 35% reduction in Rhodes Index scores.

Rhodes Index scores were analyzed as a change from baseline. At each of the 23 times at which data were collected, the Rhodes total experience score was subtracted from the baseline score to identify how the follow-up score related to the patient's pretreatment score at each time. These changes from baseline score were averaged for each patient over time and were identified as the time-averaged change in Rhodes Index total experience. A time-averaged difference was chosen because it best describes the main feature of interest, to achieve consistent reduction in nausea and vomiting from baseline levels throughout the 3-week study period. Statistical comparison between the two treatment groups with respect to the time-averaged difference in total experience was performed with a two-tailed Student *t* test. No statistical adjustments were made for baseline variables.

To understand how these data trend over the relatively short duration of the trial, these data were averaged for each patient to generate weekly summaries. Average change from baseline with regard to total experience, as well as total occurrence and total distress, was summarized. Week 1 is the mean change from baseline averaged over follow-up days 1 through 6, week 2 summarizes days 7 through 13, and week 3 summarizes days 17 and 21.

Additionally, the study and control groups were compared with respect to baseline characteristics, occurrence of adverse events, medication usage, patient satisfaction, weight gain, and urinary ketones. Data were analyzed with Student *t* tests, χ^2 tests, Wilcoxon rank-sum tests, and Fisher exact tests, as appropriate. A significance level of $\alpha = 0.05$ was used for all tests.

Stepwise multiple regression analysis was performed to explore the influence of such factors as pretreatment nausea status, age, body mass index, and estimated gestational age on the time-averaged difference in total Rhodes Index score. The significance levels for entry and removal into the equation were set at 0.15. Within subjects, repeated-measures analysis of variance was performed to test the effect of time on the primary treatment outcome, time-averaged differences in total experience. Three-way analysis of variance was used with repeated measures on one factor (time) to analyze weekly changes in total experience from baseline and to explore the effect of center-to-center variation on results.

RESULTS

A total of 230 patients were enrolled in the study. Forty-three patients (18.6%) did not complete the study (22 in the study group and 21 in the control group.) Patients who withdrew from the trial were more likely to be multiparous ($P = .041$) and to have ketonuria at entry into the trial ($P = .49$.) There were no statistically significant differences in any of the other entry characteristics, including Rhodes Index scores, between completers and noncompleters. Three patients from each group withdrew due to adverse events, but only one of these was attributed to the device. This patient devel-

Table 1. Baseline Characteristics of the 187 Patients Who Completed the Trial

Characteristic	NST			Control			
	n	Mean	SD	*n*	Mean	SD	*P*
Age (y)	95	29.7	5.3	92	29.3	5.8	.592*
Gestational age (wk)	95	9.2	1.7	92	9.0	1.7	.537*
Pretreatment weight (lb)	94	148.4	34.9	92	156.1	38.5	.154*
Body mass index (kg/m^2)	94	25.0	5.2	92	25.8	6.2	.301*
Nulliparous (*n*)	34			35			
Parous (*n*)	60			57			.929†
Ethnicity (*n*)							
White	72			67			
Black	8			12			
Hispanic	11			9			.790‡
Asian	3			2			
Other	1			2			

NST = nerve stimulation therapy; SD = standard deviation.
* Two-tailed student *t* test.
† χ^2 test.
‡ Fisher exact test.

oped severe irritation at the electrode sites from an active device. Patients who completed fewer than nine form sets were considered noncompliant. Four patients in the study group and one patient in the control group were noncompliant.

Baseline characteristics of the patients who completed the trial did not demonstrate any statistically significant differences between study and control groups (Table 1). There were no significant differences in initial Rhodes Index scores, ketonuria, or urine specific gravity (Table 2). Intention-to-treat analysis was not possible because primary outcome and secondary outcome measures were not recorded for subjects who did not complete the study protocol.

The primary outcome variable, the time-averaged change in Rhodes Index total experience, was significantly better in the study group than in the control group (6.48 [95% confidence interval (CI) 5.31, 7.66] versus 4.65 [95% CI 3.67, 5.63], $P = .02$). Three-way analysis of variance revealed that although both group assignment (nerve stimulation therapy versus control) ($P = .02$) and time ($P = .01$) had significant effects on the total experience change from baseline, no effect of study site was evident ($P = .17$) Evaluations of total symptom experience, distress, and occurrence scores were analyzed at 1-week intervals after study initiation to understand how these data trend over time. This analysis demonstrated that subjects randomized to acustimulation had greater changes from baseline than did controls at each interval, indicating an improvement in symptoms (Figure 1).

Weight gain, frequency of dehydration episodes, medication use, and presence or absence of ketonuria by dipstick measurement were assessed as secondary outcome measures. Weight gain over the 3-week trial period was significantly greater in study patients when compared with the control group for the entire population studied (2.9 ± 4.7 versus 1.2 ± 5.5 lb, $P = .003$). Of women with an active device, 77% gained weight during

Table 2. Rhodes Index Scores, Urine Specific Gravity, and Incidence of Ketonuria for the 187 Patients Who Completed the Trial

Characteristic	NST			Control			
	n	Mean	SD	*n*	Mean	SD	*P*
Total experience score	95	13.5	6.0	92	12.0	5.3	.114*
Total occurrence score	95	8.8	3.6	92	8.0	3.2	.090*
Total distress score	95	4.7	2.7	92	4.0	2.3	.137*
Urine specific gravity	95	1.019	0.008	90	1.021	0.007	.158†
Ketonuria							
Negative–trace	83			82			.555‡
Small–large	12			9			

There were no statistically significant differences between groups. Abbreviations as in Table 1.
* Wilcoxon two-sample test.
† Two-tailed Student *t* test.
‡ Fisher exact test.

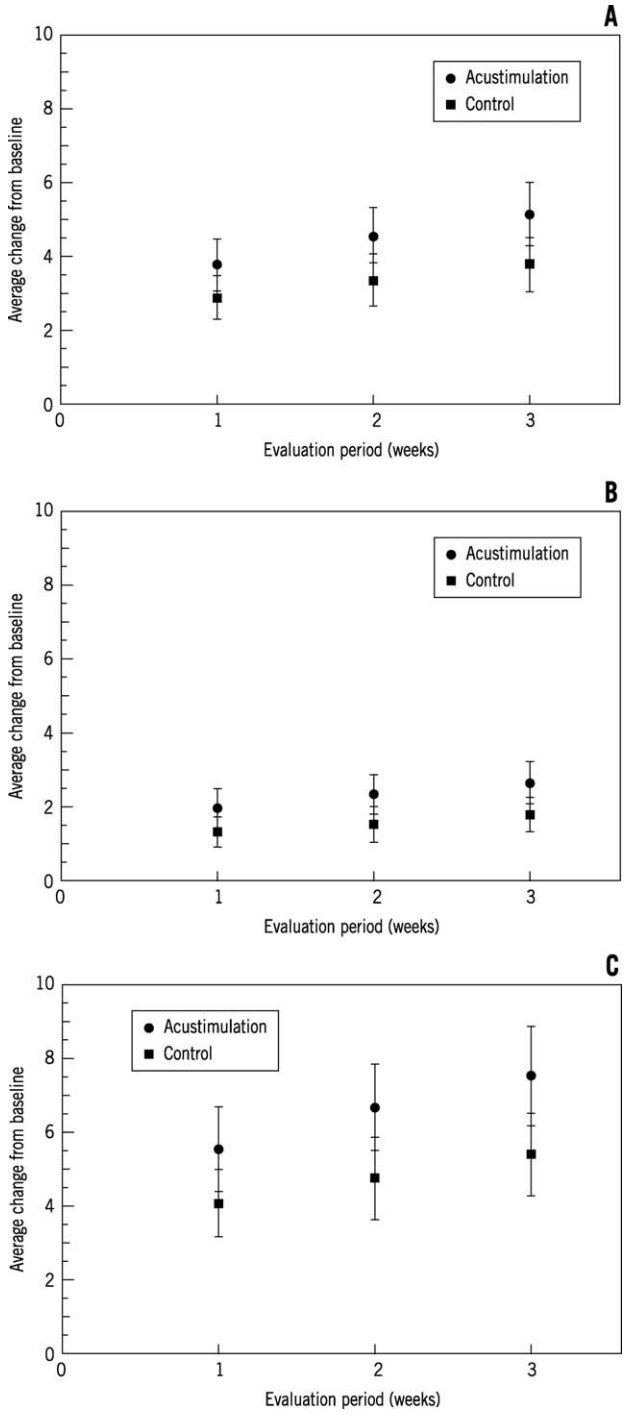

Figure 1. Weekly summaries were generated to understand how the change in Rhodes Index scores trend over time. The average change from baseline for total symptom occurrence (A), total symptom distress (B), and total symptom experience (C) during weeks 1, 2, and 3 are presented for the acustimulation and control groups. Data are presented with 95% confidence intervals. A positive change from baseline means that the patient improved incrementally from their pretreatment condition. Zero change would imply that there was no change from pretreatment. At all times, the acustimulation group presented with greater average improvement from baseline in total symptom experience, occurrence, and distress than did the control group.

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the study period, compared with 54% of controls ($P = .001$).

Fifteen occurrences of dehydration due to nausea and vomiting were reported, encompassing 2.6% (three events) of the acustimulation group and 10.6% (12 events) of the control group ($P = .013$).

There was no significant difference in the use of additional medication during the trial period. Of women in the study group, 72% did not use additional medications during the study period, compared with 75% in the control group. There were no significant differences in the number of women who used additional prescription medication between the study and control groups. The percentage of women with urinary ketones at the end of the trial was similar between the two groups (4% in study patients versus 9% of controls).

DISCUSSION

Acupuncture describes a family of procedures involving stimulation of anatomic locations on the skin by a variety of techniques and is widely practiced in the United States. Although there have been many studies addressing its potential usefulness, many of these studies have provided equivocal results because of their design and small sample size.[17] Here we report the findings of an adequately powered, prospective, randomized, placebo-controlled trial that demonstrates that acustimulation at the P6 Neiguan point is beneficial to women who suffer from symptoms of nausea and vomiting during the first trimester of pregnancy.

A major issue in interpreting trials to reduce nausea and vomiting in pregnancy is the numerous methods that have been used to assess the effectiveness of intervention. A variety of visual analogue scores, self-reporting tools, and patient interview methods have been used in previous trials. In October 1998, an expert group of clinicians determined that a standard, validated tool should be used to allow comparisons between studies, and that the Rhodes Index was an optimal tool for this purpose.[18]

The largest randomized, prospective trial of P6 acupressure, conducted by O'Brien et al,[9] also used the Rhodes Index to assess effectiveness of therapy and, in contrast to the present study, did not demonstrate a benefit. Because this trial and the current trial enrolled similar numbers of women, tested similar interventions, used the same primary outcome measure, and had different conclusions, further comparison may be valuable. It is possible that the different outcomes in these two trials can be attributed to the superiority of acustimulation over acupressure. Although the mechanism of acupuncture at the P6 point is undetermined, effects may be secondary to stimulation of the median nerve. The electrical impulses emitted by the acustimulation device tested may be capable of stimulating the nerve more intensely and reliably than is acupressure. From our experience, most users can easily detect that the band is placed properly when they feel tingling in their palm. If the device becomes dislodged, the patient loses this sensation, which should prompt them to reposition the device. In contrast, the acupressure band does not provide the same reliability with either the initial placement or with sustained use, possibly explaining the difference in effectiveness. The intensity of stimulation from the acustimulation device can also be easily adjusted, which is not possible with the acupressure band.

Alternatively, differences in methodology and patients studied may account for differences between the two trials. O'Brien et al conducted their study for 1 week, compared with 3 weeks in the current study. Indeed, whereas significant differences in total symptom experience scores were found when results were tallied over 3 weeks, significant differences in the total symptom experience or submeasures of symptom occurrence or distress were not seen observed after 1 week. The mean Rhodes Index total symptom experience scores of patients at entry into the trial were greater in the current trial than in the O'Brien trial (13.6 versus 11.0), implying that there were differences between the study groups. It is possible that acupressure would prove as effective as acustimulation in a longer trial enrolling patients with similar symptoms.

Further objective evidence of the efficacy of acustimulation for relief of nausea and vomiting symptoms was that weight gain was significantly greater in study patients when compared with controls. Interestingly, this effect was seen in women with severe symptoms who did not report reductions in Rhodes Index distress scores. One explanation for this finding could be that stimulation at P6 increases appetite. Auricular acupuncture has been reported to reduce appetite in small, uncontrolled trials,[19] but no reports of effects of acupuncture at P6 on appetite could be located with a MEDLINE search with the key words "acupuncture" and "appetite."

Future clinical trials might assess effectiveness of acustimulation combined with other nonpharmacologic therapies, such as Vitamin B6[20] or ginger,[21] which have also been shown effective in RCTs. A trial in which an acustimulation device is offered as initial therapy before other medications are prescribed might demonstrate a reduction in pharmacologic therapy where the current trial did not. The current study did not have sufficient power to assess whether efficacy of the device was related to gestational age at enrollment, and future investigation in this area may be warranted. Because of the high prevalence of nausea and vomiting in pregnancy, a

trial of acustimulation as prophylaxis against symptoms could also be rewarding.

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