

Comparison of Acustimulation and Ondansetron for the Treatment of Established Postoperative Nausea and Vomiting

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Background: This study was designed to evaluate transcutaneous electrical acupoint stimulation (acustimulation) using the ReliefBand® compared with ondansetron for the treatment of established postoperative nausea and vomiting (PONV) after outpatient laparoscopic surgery.

Methods: After the authors obtained institutional review board approval and written informed consent, 268 outpatients were enrolled in this randomized, double-blind, placebo- and sham-controlled study. All patients received antiemetic prophylaxis with metoclopramide, 10 mg intravenously, or droperidol, 0.625 mg intravenously, after induction of anesthesia. A total of 90 patients developed PONV in the recovery units and were randomized to one of three treatment groups: (1) the ondansetron group received 4 mg intravenous ondansetron and a sham ReliefBand®; (2) the acustimulation group received 2 ml intravenous saline and a ReliefBand®; and (3) the combination group received 4 mg intravenous ondansetron and a ReliefBand®. A rescue antiemetic (10 mg intravenous metoclopramide) was administered only if the PONV symptoms persisted for 15 min or longer after initiating the treatment. A blinded observer recorded the recovery times, emetic symptoms, rescue antiemetics, maximum nausea scores, complete response to study treatment, and time to achieve discharge criteria. Postdischarge side effects, as well as patient satisfaction and quality of recovery scores, were assessed at 24 and 72 h after surgery.

Results: The combination group had a significantly higher complete response rate than the acustimulation group (73% vs. 40%, $P < 0.01$). In addition, fewer patients (8 vs. 18) in the combination (vs. acustimulation) group experienced subsequent emetic events ($P < 0.03$). However, there were no significant differences between the three groups with respect to patient satisfaction and quality of recovery scores.

Conclusions: Acustimulation with the ReliefBand® can be used as an alternative to ondansetron for the treatment of established PONV. However, the use of ondansetron (4 mg intravenously) in combination with the ReliefBand® device im-

proved the complete response rate to the acustimulation therapy.

CONTROVERSY continues to surround the optimal strategy for managing the “big little problem” of postoperative nausea and vomiting (PONV).¹⁻³ For routine antiemetic prophylaxis, low-dose droperidol (0.625-1.25 mg intravenously) has clearly been demonstrated to be the most cost-effective drug.⁴⁻⁶ However, Hill *et al.*⁷ reported that ondansetron was the most effective “rescue” treatment for PONV if patients have previously received prophylaxis with droperidol or metoclopramide.

Since all antiemetic drugs can produce side effects,⁸ it has been suggested that nonpharmacologic antiemetic techniques might offer some distinct advantages over conventional pharmacologic therapies.⁹ Although a recent quantitative systematic review by Lee and Done¹⁰ confirmed that stimulation of the P6 acupoint on the median aspect of wrist can decrease PONV in adults, no study to date has directly compared acupoint stimulation to an antiemetic drug for the treatment of established PONV.

Therefore, this placebo- and sham-controlled study was designed to evaluate the use of transcutaneous electrical P6 acupoint stimulation (acustimulation) with a ReliefBand® device (Woodside Biomedical, Inc., Carlsbad, CA) as an alternative to ondansetron (Zofran®; GlaxoSmithKline, Research Triangle Park, NC) for the treatment of PONV after laparoscopic surgery in a high-risk outpatient population receiving routine antiemetic prophylaxis with low-dose droperidol or metoclopramide. The primary objective of this study was to test the hypothesis that the ReliefBand® acustimulation device alone or in combination with ondansetron was superior to ondansetron for the treatment of established PONV. A secondary objective of the study was to quantify differences in patient outcomes with respect to quality of recovery (QoR), resumption of normal activities, and satisfaction with the management of their emetic symptoms.

Materials and Methods

After we obtained institutional review board approval and written informed consent, 268 healthy outpatients scheduled for laparoscopic surgery with general anesthesia were enrolled in this study. If the patient complained

This article is featured in “This Month in Anesthesiology.”
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Received from the Departments of Anesthesiology and Pain Management and Surgery, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Submitted for publication December 20, 2001. Accepted for publication June 27, 2002. Supported by GlaxoSmithKline, Research Triangle Park, North Carolina, and Woodside Biomedical, Inc., Carlsbad, California (Dr. White). The ReliefBand® devices were provided by Woodside Biomedical Inc.

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of nausea or vomiting in the postanesthesia care unit (PACU) or in the step-down (phase II) recovery unit, they were randomly assigned to one of three treatment groups using a computer-generated random number table: (1) the ondansetron group ($n = 30$) received 4 mg intravenous ondansetron and a sham ReliefBand[®]; (2) the acustimulation group ($n = 30$) received 2 ml intravenous saline and an active ReliefBand[®]; and (3) the combination group ($n = 30$) received 4 mg intravenous ondansetron and an active ReliefBand[®].

The ReliefBand[®] is a noninvasive, portable (34 g), battery-powered (two 3V lithium coin cells), watch-like acustimulation device. The skin contact surface has two flat metal electrodes through which transcutaneous acupoint electrical stimulation is applied. Both the active and sham ReliefBand[®] devices were applied at the P6 acupoint located at the median aspect of the wrist on the dominant upper extremity (approximately 2–3 cm proximal to the distal wrist crease between the tendons of the flexor carpi radialis and the palmaris longus).¹¹ After a hypoallergenic conductive gel was applied to the skin surface, the acustimulation unit was attached around the wrist. The intensity of the current varies from 10 mA (at the starting setting #1) to 35 mA (at the maximum setting #3). The cost of the disposable ReliefBand[®] device used in this study is US \$30, whereas the reusable model costs US \$68. The acquisition cost of the ondansetron used in this study was US \$16 for a 4-mg ampule.

Two types of ReliefBand[®] devices were obtained from the manufacturer in an attempt to blind the investigators and patients as to the treatment being administered. Although all devices were identical in their external appearance (including indicator lights), the nerve stimulation therapy (NST[™]) circuitry was deactivated in the sham devices. To minimize bias resulting from the “tingling” sensation produced by the electrical stimulation, all patients were told that the ReliefBand[®] device produces a sensation that “they might or might not feel at their wrist.” None of the patients had previously used any form of acustimulation therapy. The investigators responsible for collecting these data (M.C., S.B.B., C.A.W.) were blinded to the treatment being administered to the study patients.

Patients were excluded if they had taken an antiemetic agent within 24 h prior to the operation, were pregnant, experiencing menstrual symptoms, had previous experience with acustimulation therapy, had a permanent cardiac pacemaker, or experienced vomiting or retching within 24 h before surgery. Both male and female patients were invited to participate in this study. A detailed medical history and demographic information, including age, sex, weight, height, and history of PONV, motion sickness, and cigarette smoking, were obtained from each patient. In the preoperative holding area, patients completed a baseline verbal rating scale (VRS) for nausea (from 0 = none to 10 = worst imaginable).

Patients received a standardized anesthetic consisting of propofol for induction and desflurane or sevoflurane in combination with nitrous oxide for maintenance of anesthesia. The perioperative use of opioid analgesics was also standardized and consisted of fentanyl intraoperatively, and fentanyl and morphine postoperatively. A prophylactic antiemetic (e.g., 10 mg intravenous metoclopramide or 0.625 mg intravenous droperidol) was administered to all patients after induction of anesthesia. The durations of anesthesia and surgery, as well as the lengths of stay in the PACU (phase I) and step-down (phase II) recovery unit, were recorded. Postoperative pain relief in the PACU was provided with 25- μ g or 1 mg intravenous boluses doses of fentanyl or morphine, respectively. After discharge from the PACU, pain was treated with 5 mg hydrocodone–500 mg acetaminophen administered orally.

Patients were queried as to the presence of emetic symptoms at 5–15-min intervals in the PACU, then at 30-min intervals until discharge home. The criteria for administering the antiemetic study treatment were either an emetic episode or a specific request by the patient for treatment of their nausea symptom (VRS > 3). An emetic episode was defined as one or more vomiting or retching events occurring in a rapid sequence (< 1 min between events). After reassessing their degree of nausea using the VRS, the patients were administered 4 mg intravenous ondansetron or an equal volume of intravenous saline from identical appearing syringes, and an active or sham ReliefBand[®] device was applied at the P6 acupoint as described previously.

The PACU nurses were trained in the proper positioning of the ReliefBand[®] device. Since the nurses were also blinded as to the treatment group, both the sham and active ReliefBand[®] devices were adjusted in an identical manner. All devices were started at setting #1 (lowest). If PONV symptoms persisted for 5 min, the setting was increased to # 2. If the patient was still nauseous or vomiting 5 min later, the setting was increased to #3 (highest). A rescue antiemetic (10 mg intravenous metoclopramide) was administered only if PONV symptoms persisted for 5 min with the device at the maximum setting (#3). Patients receiving the rescue antiemetic were considered to be treatment failures. All patients were asked to continue using the acustimulation device at home for up to 72 h.

Assessments to determine the presence of persistent emetic symptoms were performed at 5-, 10-, 15-, 20-, 30-, 60-, 90-, and 120-min intervals after starting the study treatment. To meet the discharge criteria, the patient had to be awake and alert, with stable vital signs while standing, be able to walk without assistance, and not actively experiencing side effects. Prior to discharge, patients were asked if they felt a tingling sensation in the upper extremity to which the acustimulation device was applied.

Table 1. Patient Demographic Characteristics, Duration of Anesthesia and Surgery, Type of Antiemetic Prophylaxis and Time to Study Treatment in the Three Study Groups

	Ondansetron (n = 30)	Acustimulation (n = 30)	Combination (n = 30)
Age (yr)	35 ± 9	42 ± 16	42 ± 15
Height (cm)	163 ± 12	162 ± 11	163 ± 12
Weight (kg)	74 ± 13	80 ± 24	80 ± 21
Sex (M/F) (n)	2/28	2/28	3/27
ASA (1/2/3) (n)	12/18/0	10/19/1	10/18/2
Type of surgery: [n (%)]	—	—	—
Laparoscopic cholecystectomy	23 (77)	22 (75)	23 (77)
Gynecologic laparoscopy	7 (23)	8 (25)	7 (23)
Previous surgery [n (%)]	17 (57)	25 (83)	20 (67)
H/o PONV [n (%)]	7 (23)	8 (27)	8 (27)
H/o motion sickness [n (%)]	2 (7)	4 (13)	9 (30)*
H/o dizziness [n (%)]	5 (17)	4 (13)	9 (30)
Non-smokers [n (%)]	23 (77)	21 (70)	25 (83)
Preoperative nausea score (0–10)	0	0	0
Anesthesia time (min)	111 ± 60	118 ± 61	125 ± 58
Surgery time (min)	83 ± 59	87 ± 55	98 ± 57
Antiemetic prophylaxis [n (%)]	—	—	—
Metoclopramide, 10 mg IV	9 (30)	8 (27)	4 (13)
Droperidol, 0.625 mg IV	21 (70)	22 (73)	26 (87)
Time from end of anesthesia to treatment (min)	58 ± 51	79 ± 78	74 ± 72

Values are mean ± SD, or number (n) and percentages (%)

* Significantly different from the Ondansetron group, $P < 0.05$

ASA = American Society of Anesthesiologists; PONV = postoperative nausea and vomiting

When patients were discharged from the hospital, they were allowed to take the device home and were requested to keep it on their wrist for the next 72 h except when bathing. Follow-up telephone calls were made to all patients at 24 and 72 h postoperatively to determine the incidence of PONV after discharge and to assess the patient's satisfaction with their QoR from anesthesia (using a VRS, from 0 = poor recovery to 10 = excellent recovery) and their satisfaction with the antiemetic treatment (using a VRS, from 0 = very dissatisfied to 100 = highly satisfied). Patients were also queried regarding the time required to resume a normal diet, normal daily activities, and a regular sleep pattern.

Statistical Analysis

An *a priori* power analysis determined that a sample size of 26 patients in each group would be adequate to detect a 30% absolute decrease (from 40 to 10%)⁸ in the need for antiemetic rescue medication after initiating the study treatment between the three groups ($\alpha = 0.05$), with a power of 80%. Data were analyzed with the Number Cruncher Statistical System version 6.0 (NCSS, Kaysville, UT). A one-way analysis of variance was used for all continuous variables, with the Bonferroni test performed for *post hoc* intergroup comparisons. Categorical data were analyzed by using the chi-square test. The VRS scores were analyzed by the Kruskal-Wallis test. If a significant difference was obtained, the Wilcoxon rank sum test was performed. The time to recurrence of emetic symptoms ("rescue") after the study treatment was analyzed using the log-rank test statistics. The times

to when 25% of the patients in each group were judged to have failed the antiemetic study treatment (*i.e.*, when 10 mg intravenous metoclopramide had to be administered as a rescue antiemetic) were determined by the Kaplan-Meier method. Data were presented as means ± SD, medians, numbers, or percentages, with $P < 0.05$ considered statistically significant.

Results

Of the 268 patients enrolled in the study, 90 (34%) complained of nausea or experienced an episode of vomiting or retching within the first 2 h after admission to the recovery unit and were entered into the treatment protocol. Postdischarge data were obtained from 83 of the 90 study patients at 24 and 72 h. All of these patients reported that they continued to use the ReliefBand[®] after discharge. Demographic characteristics for the three treatment groups, including VRS nausea scores at the time the antiemetic treatment was initiated, were not significantly different (tables 1 and 2). However, a significantly larger percentage of patients in the combination (*vs.* ondansetron) group had a history of motion sickness (30% *vs.* 7%, respectively; $P < 0.01$). The three treatment groups did not differ with respect to durations of surgery and anesthesia, as well as times to receive the first dose of opioid analgesic medication and to initiate the antiemetic treatment in the postoperative period (tables 1 and 2). Finally, there was no difference in the percentage of patients in each treatment group receiving

Table 2. Recovery Times, Time to First Analgesic and Antiemetic Rescue Therapy, Time from ReliefBand® application to rescue antiemetic treatment, Complete Response and Hospital Admission Rate, and Highest Nausea Score prior to Discharge in the Three Treatment Groups

	Ondansetron (n = 30)	Acustimulation (n = 30)	Combination (n = 30)
PACU time (min)	62 ± 37	63 ± 28	70 ± 36
Phase II unit time (min)	145 ± 73	184 ± 91	196 ± 91*
Oral intake time (min)	133 ± 66	131 ± 71	137 ± 60
Ambulation time (min)	185 ± 62	169 ± 84	175 ± 53
Voiding time (min)	187 ± 68	151 ± 82	169 ± 66
First dose of opioid medication (min)	60 ± 62	44 ± 49	58 ± 54
Postoperative opioids administration [n (%)]	20 (67)	15 (50)	15 (50)
Baseline nausea score (0–10)	6 (4–10)	5 (3–10)	6 (4–10)
Time from treatment to rescue antiemetic (min) (n)	51 ± 43 (13)	63 ± 53 (18)	58 ± 37 (8)†
Complete response at 2 h [n (%)]	17 (57)	12 (40)	22 (73)‡
Post-treatment retching [n(%)]	10 (33)	8 (27)	10 (33)
Post-treatment vomiting [n(%)]	10 (33)	17 (57)	8 (27)‡
Side effects requiring treatment at PACU [n(%)]	—	—	—
Pruritus	1 (3)	0	0
Difficulty voiding	1 (3)	1 (3)	0
Headaches	0	0	0
Dizziness	0	1 (3)	0
Fit for discharge (min)	191 ± 53	209 ± 83	219 ± 87
Required hospital admission [n (%)]	5 (17)	6 (20)	6 (20)
Admitted for PONV [n (%)]	0	0	0
Highest nausea score (0–10)	5 (0–8)	5 (0–10)	6 (0–10)
Patient felt tingling sensation [n (%)]	9 (30)	17 (57)	19 (64)

Values are mean ± SD, or number (n) and percentages (%).

* Significantly different from the Ondansetron group, $P < 0.05$; † Significantly different from the Acustimulation group, $P < 0.05$ (number of patients only);

‡ Significantly different from the Acustimulation group, $P < 0.05$.

PACU = postoperative anesthesia care unit; Phase II unit = step-down unit; PONV = postoperative nausea and vomiting.

opioid analgesics in the PACU and phase II recovery units.

With respect to emetic symptoms prior to discharge from the hospital, there were no significant differences between the ondansetron and acustimulation groups (table 2). However, within the first 2 h after initiation of the antiemetic treatment, significantly more patients receiving the combination therapy had no complaints of nausea or episodes of vomiting-retching (*i.e.*, complete response) compared with patients receiving the ReliefBand® alone (22 *vs.* 12; $P < 0.01$). In the predischARGE period, significantly fewer patients in the combination group experienced vomiting compared with the acustimulation group (8 *vs.* 17; $P < 0.03$).

The times to voiding, ambulating, and being judged “fit for discharge” did not differ among the three groups (table 2). In addition, there was no significant difference in the incidence of side effects reported in the PACU and step-down units (table 2). The times to resumption of normal diet and physical activity during the 72-h study period did not differ among the three groups (table 3). Surprisingly, a higher percentage of patients in the acustimulation (*vs.* ondansetron) group reported a regular sleep pattern at 24 h after surgery (70% *vs.* 33%). The QoR scores and degree of patient satisfaction with the management of their emetic symptoms was found not to differ among the three treatment groups (table 3). In comparing the “fit for discharge” times, QoR and patient

satisfaction scores in patients who did (199 ± 72, 7 ± 2, and 93 ± 12) or did not (217 ± 80, 7 ± 2, and 91 ± 14) have a complete response, no statistically significant differences were found.

Finally, the Kaplan-Meier estimates suggests that the median time to 25% of the patients in the combination group requiring additional (rescue) antiemetic therapy was significantly longer (110 min) compared with the ondansetron (45 min) and acustimulation (26 min) groups (fig. 1).

Discussion

In a high-risk outpatient population undergoing laparoscopic surgery, 34% developed PONV despite prophylaxis with either droperidol (0.625 mg administered intravenously) or metoclopramide (10 mg administered intravenously). The efficacy of the ReliefBand® did not differ significantly from ondansetron (4 mg administered intravenously) as a treatment for established PONV. Although the complete response rate at 2 h after initiating the treatment was slightly higher in the ondansetron (*vs.* acustimulation) group, the patients’ satisfaction and their assessment of the QoR were similar in these two study groups.

The complete response rate was significantly higher with the combination therapy compared with the Relief-

Table 3. Side Effects Reported during the 72 h Study Period and Patient Satisfaction Scores in the Three Treatment Groups

	Ondansetron (n = 27)	Acustimulation (n = 29)	Combination (n = 27)
At 24 h follow-up evaluation	—	—	—
Nausea [n (%)]	18 (67)	12 (40)	12 (45)
Vomiting [n (%)]	7 (26)	8 (26)	6 (21)
Normal sleep [n (%)]	9 (33)	20 (70)*	13 (48)
Return to normal activities [n (%)]	0	2 (7)	1 (4)
Resume normal diet [n (%)]	9 (33)	12 (40)	8 (28)
Highest nausea score (0–10)	3 (0–10)	0 (0–10)	0 (0–10)
At 72 h follow-up evaluation	—	—	—
Nausea [n (%)]	4 (13)	6 (19)	3 (11)
Vomiting [n (%)]	1 (4)	3 (11)	0
Normal sleep [n (%)]	16 (58)	23 (81)	22 (82)
Return to normal activities [n (%)]	5 (20)	11 (39)	8 (29)
Resume normal diet [n (%)]	21 (80)	23 (81)	21 (80)
Highest nausea score (0–10)	0 (0–4)	0 (0–1)	0 (0–3)
QoR score (0–10)	7 (5–10)	8 (2–9)	8 (5–10)
Patient satisfaction score (0–100)	95 ± 17	91 ± 11	94 ± 11

Values are mean ± SD, medians (ranges), or number (n) and percentages (%). QoR: (0 = poor recovery to 10 = excellent recovery); Patient satisfaction: 0 = very dissatisfied to 100 = highly satisfied.

* Significantly different from the Ondansetron group, $P < 0.05$.

QoR = quality of recovery score.

Band[®] alone (73% *vs.* 40%), suggesting that ondansetron enhanced the efficacy of acustimulation in the treatment of PONV. The benefits of the combination therapy may have been even greater than we reported because this group had a significantly higher percentage of patients with a history of motion sickness, a well-known risk factor for PONV.^{12,13} The typical response rate to placebo (saline) treatment for “established” PONV ranges from 14 to 20%.^{14,15} According to a recent quantitative systematic review evaluating the efficacy of the 5-HT₃ receptor antagonists in the treatment of established PONV,¹⁶ the authors suggested that “20–30% of patients receiving a 5-HT₃ antagonist will stop vomiting who

would not have done so had they received a placebo.” Given the low placebo response rate and the documented antiemetic efficacy of ondansetron in treating established PONV, our surgeons and anesthesiologists did not feel it was ethical to administer a “placebo” to patients who developed active PONV after receiving standard antiemetic prophylaxis with droperidol or metoclopramide.

Previous placebo-controlled studies have found similar complete response rates with ondansetron (57%)¹⁵ and dolasetron (53%).¹⁷ Given the current trend toward a higher complete response rate in the ondansetron (*vs.* acustimulation) group, a *post hoc* power analysis suggested that group sizes in excess of 117 patients each (requiring the enrollment of > 1,000 additional patients) would be necessary to find a significant difference between these two treatment groups assuming that the response rates remained constant and the overall incidence of the emetic symptoms after laparoscopic surgery at our teaching institution remained unchanged (34%).

It is also possible that the antiemetic efficacy of acustimulation would have been enhanced if it had been applied before (*vs.* after) surgery.¹⁸ Further studies are clearly needed to evaluate the effect of timing (preoperative *vs.* postoperative) on the antiemetic efficacy of the ReliefBand[®] device. Although both the patients and the investigators recording these data were “blinded” as to the treatment group, a higher percentage of patients in the active acustimulation groups were aware of the tingling sensation produced by the ReliefBand[®] device, suggesting that the patients may have been aware that they were or were not receiving the “active” acustimulation treatment. Therefore, it is possible that the pa-

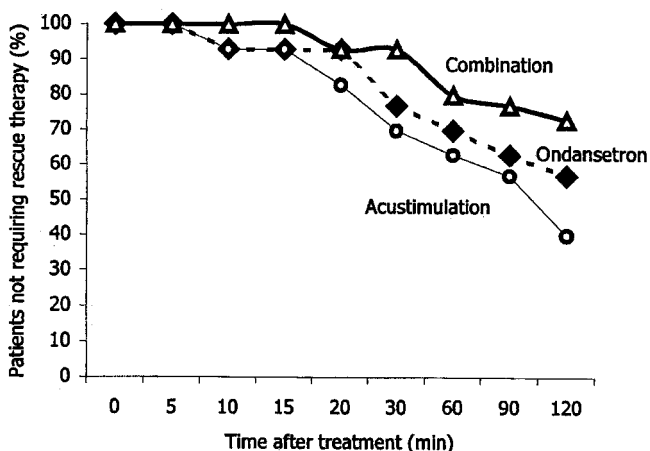


Fig. 1. Kaplan-Meier estimates demonstrating the time to “rescue” with metoclopramide after initial treatment of established postoperative nausea and vomiting (PONV) with ondansetron (n = 30), acustimulation (n = 30), or combination (n = 30) therapy. Compared with the combination group, significantly more patients in the acustimulation group required a rescue antiemetic within the first 2 h after initiating the study treatment ($P < 0.05$).

tients may have been biased in favor of the active (*vs.* sham) acustimulation treatments. Although the application of the ReliefBand® device at the P6 acupoint may produce an acupressure-type response, this effect would have been present to an equal extent in all three groups.

The current findings with ondansetron (4 mg administered intravenously) are consistent with the results of single- and multicenter, placebo-controlled studies involving the use of intravenous ondansetron for treating established postoperative emesis in children and adults.^{14,19,20} The complete response rates at 24 h after ondansetron administration was 53% (*vs.* 17%) and 41–47% (*vs.* 15%) for the ondansetron (*vs.* placebo) groups in the pediatric¹⁹ and adult²⁰ studies, respectively. Consistent with the findings of Hill *et al.*,⁷ prophylaxis with droperidol or metoclopramide did not appear to alter the response to ondansetron treatment. Ondansetron was selected as the comparator drug because the majority of the patients (77%) had received low-dose droperidol for prophylaxis, and controversy surrounds the use of droperidol for treatment of PONV.²¹

The relatively small group sizes ($n = 30$) may have contributed to our inability to find any clinically significant differences among the three study groups with respect to posttreatment side effects. Previous studies with the ReliefBand® have reported that it can produce localized erythema in some patients,²² and ondansetron has been associated with an increased incidence of headaches and changes in hepatic enzymes.^{8,23} Of interest, a recent case report described the occurrence of acute myocardial ischemia after the intravenous injection of ondansetron for treatment of intractable nausea.²⁴ However, studies involving larger group sizes would be necessary to demonstrate significant differences in side effects among the three treatment groups.

We conclude that the use of the ReliefBand® acustimulation device may be an acceptable alternative to ondansetron for the treatment of established PONV. In addition, ondansetron appears to enhance the efficacy of the ReliefBand® in the management of emetic symptoms after outpatient laparoscopic surgery.

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