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Randomized double-blind study of the Reliefband as an adjunct to standard antiemetics in patients receiving moderately-high to highly emetogenic chemotherapy

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Abstract *Goals:* Our goal was to evaluate the efficacy and tolerability of the Reliefband as an adjunct to standard antiemetics in patients receiving moderately-high to highly emetogenic chemotherapy. *Patients and methods:* Forty-nine adult cancer patients receiving moderately-high or highly emetogenic chemotherapy were randomized to receive either the active Reliefband (n=26) or an inactive device (n=23). Patients continued to receive all scheduled and as needed antiemetic agents as prescribed. The device was worn the day of chemotherapy administration for 5 days (days 1–5). Patients maintained a daily dairy of nausea severity, vomiting and retching episodes, and antiemetic medications taken. Each patient completed a Functional Living Index Emesis (FLIE) and a tolerability survey at the conclusion of the study. A Wilcoxon rank sum test was used to compare the number of vomiting episodes, severity of nausea and FLIE scores between the two groups. *Main results:* Patients wearing the active Relifband experienced less vomiting (Reliefband 1.9 versus inactive device 4.6 mean episodes; p=0.05), retching (1.4 versus 3.6 mean episodes; p=0.05), and nausea severity (0.91 versus 1.65 mean cm/day; p=0.01) over the 5-day period compared to patients wearing the inactive device. Vomiting was statistically significantly reduced during the delayed period (0.42 versus 1; p=0.032), whereas nausea was significantly reduced during the acute (0.71 versus 2.3; p=0.028) and delayed (1.8 versus 3.3; p=0.020) periods. FLIE scores did not differ between the two treatment groups (91 versus 80; p=0.088). *Conclusions:* This study suggests that patients receiving moderately-high to highly emetogenic chemotherapy who experience nausea and vomiting despite scheduled antiemetics may benefit from the use of the Reliefband as an adjunct to antiemetics. Limitations of this study include differences in risk factors for emesis, chemotherapy, and antiemetic regimens. A larger, better, controlled randomized study is needed to better define optimal use of this device.

Keywords Acustimulation · Transcutaneous electrical stimulation · Acupressure · Nausea · Vomiting · Chemotherapy · Reliefband

Introduction

Chemotherapy induced nausea and vomiting (CINV) are two of the most commonly reported adverse effects of chemotherapy [16]. Uncontrolled CINV reduces quality of life [23, 26], leads to delays in treatment [22], and causes serious metabolic disturbances.

Current strategies for preventing acute CINV include combination therapy with a 5-HT_3 antagonist and a corticosteroid for moderately-high to highly emetogenic chemotherapy [15, 28]. Similarly, strategies aimed at reducing the incidence and severity of delayed CINV include the combination of a corticosteroid and either a dopamine receptor antagonist or a 5-HT_3 antagonist for 3–5 days post chemotherapy [15, 28]. Complete protection from vomiting in the first 24 h is achieved in as many as 70–90% of patients receiving moderately-high and highly emetogenic chemotherapy; however, standard antiemetics only protect 50% of patients from experiencing nausea during this acute CINV phase [31, 18]. Delayed nausea and vomiting is less well defined and controlled, with as many as 50% of patients experiencing nausea and vomiting in the 3 to 5 day period following the first day of chemotherapy [18, 2]. Both acute and delayed CINV remain a significant problem in patients undergoing high-dose chemotherapy for autologous or allogeneic transplantation where up to 90% of patients experience CINV despite prophylactic strategies [27, 1, 4].

Additional pharmacological interventions are clearly needed to optimize control of CINV. Neurokinin-1 receptor (NK-1) antagonists have been reported to improve the total control rates of acute CINV by approximately 25% compared to the standard combination of a 5-HT_3 antagonists and dexamethasone alone [24, 6]. Cocquyt et al. [7] reported that one dose of a NK-1 antagonist administered prior to cisplatin-based chemotherapy prevented delayed emesis in up to 72% of patients. Although promising, the role of these agents in CINV prevention and control is as yet undetermined.

Acupuncture constitutes a nonpharmacological intervention for CINV. Chinese medicine holds that stimulating select points on the body, that lie along meridians or life channels, can relieve diseases [32]. Traditional acupuncture is an invasive procedure that uses fine needles inserted into specific points on the body to achieve a certain therapeutic effect. The P6 point, also known as the Neiguan point or G-Jo point no. 10, is located 2 cun (Chinese inch, equivalent to the width of an individual's thumb) proximal to the distal wrist crease, between the tendons of the palmaris longus and flexor carpi radialis [19]. P6 acupuncture was shown to reduce the incidence and severity of nausea and vomiting in the postoperative setting, morning sickness, and CINV [5, 8, 9, 10, 11, 30].

Less invasive stimulation of the P6 point can be achieved in the form of a transcutaneous electrical stimulation (TCES). P6 TCES therapy was shown to enhance the antiemetic action of ondansetron in patients receiving highly emetic chemotherapy treatment [5, 13, 29]. The Reliefband is a class-2 device cleared by the FDA for the treatment of nausea and vomiting due to chemotherapy, motion sickness, pregnancy, and AIDS therapy. The device delivers slow, weak, electrical pulses to the P6 point through a simple wristband device. The electrical output can be adjusted by the patient to deliver 10–35 mAmps/pulse. Pulses are conducted to the P6 point via two metallic electrodes. In a placebo-controlled study of gynecologic oncology patients receiving platinum-based therapy, patients randomized to apply the active Reliefband experienced less severe nausea than those randomized to inactive devices [29].

The objectives of the study described were to evaluate the efficacy and patient acceptance of the Reliefband as an adjunct to standard antiemetics in patients receiving emetogenic chemotherapy.

Patients and methods

Study design

This was a randomized, prospective, double blind, placebo-controlled trial approved by the institutional review board at the University of North Carolina at Chapel Hill School of Medicine and the Lineberger Comprehensive Cancer Center protocol review committee.

Patients and eligibility

Adult cancer patients admitted to University of North Carolina Hospitals to receive single or multiple day chemotherapy regimens classified as moderately-high (at least one level 4 agent) or highly (at least one level 5 agent) emetogenic based on our previously published classification system [20] were eligible to participate in this trial. These included patients receiving myeloablative chemotherapy for bone marrow transplantation, acute leukemia induction, or solid tumor regimens. Life expectancy of greater than 3 months and an ECOG performance status of less than three were additional inclusion criteria. Patients were excluded if they were using permanent cardiac pacemakers, were unable to read and write, or unable to provide informed consent. All eligible patients provided informed consent prior to randomization.

Antiemetic therapy

All patients were premedicated each day that moderately-high and highly emetogenic chemotherapy was administered in accordance with the institution's approved guidelines. Acute CINV prophylactic regimens included oral (24 mg) or intravenous (8 mg) ondansetron and either oral or intravenous dexamethasone (20 mg) given 30 min prior to chemotherapy. Delayed CINV prophylaxis consisted of oral dexamethasone (8 mg BID) in addition to prochlorperazine (15 mg spansules BID) or oral ondansetron (8 mg BID). Rescue medications included metoclopramide or droperidol prescribed as needed at the discretion of individual treating physicians.

Patients were randomized to wear either an active Reliefband or an identically appearing inactive device for 5 days commencing with chemotherapy. The electrical circuit in the inactive device

was disabled by the manufacturer. Reliefband and inactive devices were supplied by Woodside Biomedical, Inc. An unblinded study investigator instructed patients on the proper placement and use of the active and inactive Reliefband. Electrodes of the Reliefband were placed on the inner surface of the wrist to deliver TCES to the P6 point as described previously [13]. Correct stimulation of the P6 point produces a nonanatomically distributed sensation going up the arm or into the fingers, which patients randomized to the active device were instructed to monitor [13]. Patients randomized to the inactive Reliefband were told that they may or may not feel the effect of the Reliefband. TCES by the Reliefband to the P6 point was facilitated by means of a colorless, odorless, conductivity gel that was applied every 6 h while the patients were awake. Patients wore the devices continuously for 5 days, except during showering and hand washing.

Data collection

Prestudy assessments included prior chemotherapy regimens, history of CINV, motion sickness, and hyperemesis gravida. The number of vomiting and retching episodes, severity of nausea, and use of rescue medications were recorded in a daily diary [23]. Severity of nausea was assessed using a 10-cm horizontal visual-analogue scale where the zero-cm mark was labeled with "no nausea" while the 10-cm mark was labeled "nausea as bad as could be." Patients maintained the diary for the 5 days they were wearing the device. To assess the impact of the Reliefband on quality of life, patients were asked to complete the Functional Living Index-Emesis (FLIE) [23] on the last day of the study. The FLIE questionnaire is an emesis- and nausea-specific quality-of-life questionnaire developed and recently validated for 5-day recall period for measuring the characteristics of CINV [21]. A blinded investigator visited patients daily to ensure appropriate completion of the daily diary and to verify diary entries by comparing patient-reported data to medication administration records (MAR) and progress notes.

Statistical analysis

The median number of episodes of vomiting, mean severity of nausea, and mean FLIE scores of the two groups were compared. Wilcoxon rank sum test was used to measure the significance of the difference between active and inactive arms in episodes of emesis and retching and severity of nausea. Fisher's exact *t*-test was used to analyze differences in rates of complete protection from CINV. All data is reported as mean plus or minus standard deviation.

A sample size of 20 patients in each arm provided the study, with 80% power to detect a difference of two emetic episodes between the two arms with a predicted standard deviation of one emetic episode and one-sided alpha of 0.05.

Results

Patients

Forty-nine patients were enrolled in this study. Five patients, two in the active device group and three in the inactive devise group were excluded from data analysis. Two patients withdrew due to malfunction of the device; one patient did not wear the device on day 1 due to miscommunication, and two patients were excluded due to incomplete documentation. Demographic characteristics of patients randomized to the active and inactive device groups were similar (Table 1).

Table 1 Demographic characteristics of patients randomized to active and inactive

Characteristic	Active band	Inactive band
Patients (*n*)	24	20
Male/female (*n*)	12/12	11/9
Age (median, range)	46	44
Diagnosis (*n*)		
Breast cancer	3	1
Head and neck cancer	6	1
Leukemia	4	4
Lung cancer	2	1
NonHodgkin's lymphoma	3	7
Sarcoma	2	2
Other	4	4
History of motion sickness (*n*)	21	15
Nausea with pregnancy (*n*)	6	3
Concomitant radiation	10	7
Prior chemotherapy cycles	3.5	4.5

Table 2 Treatment characteristics of patients randomized to active and inactive devices

Chemotherapy regimen	Device	
	Active	Inactive
Bone marrow transplantation conditioning regimens	7	9
Platinum regimens	15	11
Cyclophosphamide/Ifosfamide	4	9
High-dose cytarabine	2	4
Dacarbazine	1	2
Anthracyclines	5	2
Melphalan	3	0
Vinblastine	1	1

Patients in both groups received similar regimens in terms of chemotherapy agents, dose, and duration (Table 2). Despite randomization, however, a disproportionate number of patients in the inactive device group received cyclophosphamide-based regimens (eight versus one). Median duration of chemotherapy was 3 days in both groups. Table 2 illustrates some of the chemotherapy agents administered to the patients.

Efficacy

The mean number of vomiting episodes over days 1–5 in the active device group was lower than the inactive device group (1.9 versus 4.6 episodes; p=0.05). Similarly, the mean number of retching episodes during days 1–5 was significantly reduced for patients wearing the active

Table 3 Efficacy of Reliefband during days 1–5

Parameter	Active	Inactive	*p*
Vomiting episodes	1.9±3.2	4.6±6.5	0.050
Retching episodes	1.4±2.6	3.6±6.6	0.049
Severity of nausea	1.54±1.7	3.1±2.6	0.018
Doses of breakthrough medications	0.91±1.6	1.65±1.6	0.17

Table 4 Efficacy of Reliefband for active and delayed chemotherapy induced nausea and vomiting (CINV) periods

Parameter	Active	Inactive	*p*
Acute CINV (Day 1)			
Emetic episodes	0.26±0.56	0.67±1.3	0.250
Nausea score (mean cm/day)	0.71±1.6	2.3±3.1	0.028
Delayed CINV (Days 2–5)			
Emetic episodes	0.42±0.77	1±1.4	0.032
Nausea score (mean cm/day	1.8±2	3.3±2.6	0.020

device compared to patients wearing the inactive device (1.4 versus 3.6 episodes; p=0.05). Patients wearing the active device reported less nausea using the visual analog scale over the 5-day period than patients randomized to the inactive device group (0.91 versus 1.65 mean cm/day; p=0.018). Overall, the active device provided approximately a 50% reduction in the incidence and severity of emesis and nausea respectively (Table 3).

The difference in the mean number of emetic episodes was not statistically reduced in the acute CINV setting. However, the difference in the mean number of emetic episodes in the delayed CINV setting was reduced for patients wearing the active Reliefband (0.42 versus 1; p=0.032). Similarly, the active Reliefband reduced the severity of nausea in the acute (0.71 versus 2.3 mean cm/day; p=0.028) and delayed setting (1.8 versus 3.3 mean cm/day; p=0.020) (Table 4).

Additionally, the active Reliefband increased the proportion of patients who had complete protection from nausea during days 1–5 (41% versus 15%; p=0.064) and the proportion of patients with a nausea score <3 on the 10-cm VAS (73% versus 45%; p=0.065).

Quality of life analysis

Thirty-three patients completed the FLIE quality-of-life assessment. There was no statistically significant difference between the total FLIE scores reported for patients wearing the active or inactive device (91 versus 80; p=0.088).

Safety analysis

No patient discontinued the study for reasons related to active or inactive Reliefband toxicity. Only two patients wearing the active Reliefband reported side effects: the first reported a shocking sensation in the arm, and the second tingling in the fingers and irritation under the active Reliefband. No side effects were reported by patients wearing the inactive device.

Discussion

CINV remains a major concern for patients undergoing chemotherapy. Although 5-HT_3 antagonists markedly reduced the incidence and severity of CINV with moderately-high to highly emetogenic chemotherapy regimens, this study, like many others, has again demonstrated that patients continue to experience significant CINV, especially in the delayed setting.

Use of the active Reliefband as an adjunct to standard antiemetics significantly reduced the incidence of chemotherapy induced emesis. The mean number of emetic episodes in the delayed setting was reduced more than 50% by the active Reliefband compared to the inactive device. The active Reliefband did not improve on the control rates of vomiting in the first 24 h due, perhaps, to the low incidence of emesis in this period observed in both groups. However, it did increase the proportion of patients who achieved complete control of vomiting on days 2–5 by 25%, although the difference did not achieve statistical significance (p=0.077).

The benefit of the active Reliefband on the severity of nausea was demonstrated during the first 24 h and in the 4 days following chemotherapy administration. The active Reliefband significantly reduced mean nausea scores in the delayed setting compared to the inactive device by approximately 50%. Similarly, the active Reliefband significantly reduced the mean nausea scores in the first 24 h compared to the inactive device (p=0.02).

Although there was a marked reduction in the incidence and severity of vomiting and nausea with the active Reliefband, improvements in the FLIE quality-of-Life scores did not reach statistical significance (91 versus 80; p=0.088). Of note, due to the acuity of the patients enrolled in this study, the FLIE scores were significantly lower than FLIE scores reported from other trials [21, 23, 1].

A weakness of the study is the inclusion of a diverse group of patients receiving a wide range of chemotherapy and antiemetic regimens. This has two consequences: (1) potential for imbalances in the two treatment group despite randomization, and (2) variation in response observed between both groups clearly reduced the power of the study to find a significant difference between them. Blinding patients in trials that include the Reliefband is

difficult, because patients wearing the active Reliefband feel the electrical stimulation at the P6 point. This sensation is not felt by those wearing the inactive device. To the extent possible, this was controlled for by using an unblinded investigator to provide device-specific instructions, which specified that an impulse was not expected when the inactive device was worn.

This study, along with other studies [29, 5], demonstrates the efficacy of the Reliefband in decreasing the incidence and severity of CINV when used as an adjunct to standard antiemetics in patients receiving moderately-high to highly emetogenic chemotherapy. High-risk patients may be offered this noninvasive treatment to minimize CINV do to moderately-high to highly emetogenic chemotherapy regimens despite receiving standard scheduled antiemetic medications. The limitations of this study have been noted, and large multicenter trials are needed to determine the specific role of the Reliefband in CINV.

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