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Original Article

Auricular point acupressure improved nausea, vomiting, diarrhea and nutritional status in gastric cancer patients receiving oral S-1 therapy

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Abstract: Objective: This study explored the efficacy of auricular point acupressure (APA) on controlling gastrointestinal dysfunction and improving nutritional status in gastric cancer patients receiving oral S-1 treatments. Methods: One-hundred and ten gastric cancer patients who received oral S-1 therapy were enrolled and randomized into two sub-cohorts (1:1). In the experimental sub-cohort, specific auricular points were stimulated to control nausea, vomiting, and diarrhea, including the shenmen, cardia, stomach, sympathetic, digestive subcortex, liver, and spleen. The auricular points that were stimulated in the control cohort included the eye, wrist, toe, and external genitals. Patients wore auricular seeds for 21 days and recorded instances of nausea, vomiting, and diarrhea using the National Cancer Institute common toxicity criteria as benchmarks. Weight, height, total blood protein, and albumin levels were measured twice per patient at the start and end of the experimental course. Results: Incidence rates of nausea, vomiting, and diarrhea were similar between the two sub-cohorts ($p>0.05$). Patients in the experimental sub-cohort experienced lower severities and shorter durations of nausea, vomiting, and diarrhea when compared to controls ($p<0.05$). Additionally, patients in the experimental sub-cohort experienced less dramatic reductions in nutrition indices, including body weight, body mass index, total blood protein, and albumin levels ($p<0.05$). Conclusions: The data presented here indicate that APA treatment decreased the severity and duration of nausea, vomiting and diarrhea in gastric cancer patients receiving oral S-1 chemotherapy. This treatment may improve the nutritional status of treated patients. However, incidence rates of S-1 treatment-related side effects were unaltered by APA.

Keywords: Auricular point acupressure, chemotherapy, nausea, vomiting, diarrhea, nutrition

Introduction

Gastric cancer is the fourth most common cause of cancer morbidity and the third leading cause of cancer-specific deaths worldwide [1]. In 2016, it was estimated that approximately 26,370 new cases were diagnosed and 10,730 patients died in the United States [2]. First-line treatment for early gastric cancer is curative surgery, but the cancer relapse rate is relatively high when using surgery alone [3, 4]. A meta-analysis indicated that the addition of adjuvant chemotherapy to surgery provided clinical benefit for gastric cancer patients [5]. A widely used postoperative adjuvant chemotherapy protocol includes combination therapy with S-1 and oxaliplatin (SOX) [6, 7]. While SOX has therapeutic efficacy, use of this therapy also has concomitant adverse effects, including neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, asthenia and neurotoxicity [6]. Serotonin (5-HT3) antagonists, glucocorticosteroids, phenothiazines, berberine hydrochloride, montmorillonite powder and loperamide agents are utilized to control nausea, vomiting and diarrhea. While application of these drugs can effectively reduce symptoms, these agents also have side effects such as mood disturbances and drowsiness [8]. Additionally, glucocorticosteroids may reduce anti-tumor effects of some chemotherapeutic agents [9]. When S-1 is delivered orally at home, it may be challenging

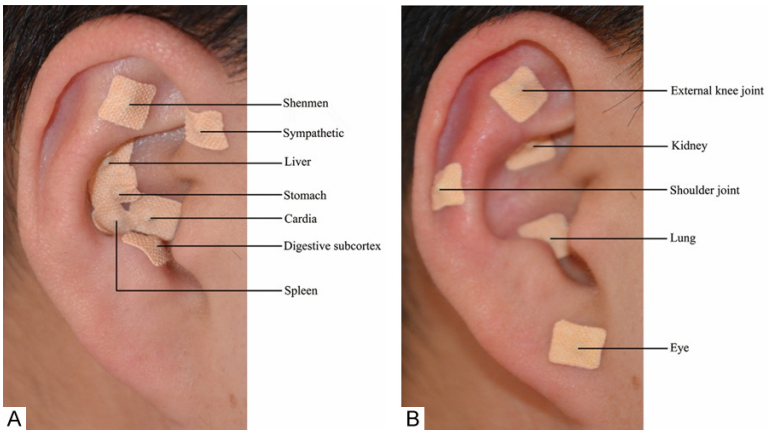

Figure 1. Locations of ear acupoints in the experimental sub-cohort (A) and control sub-cohort (B).

for patients to seek professional help for side effects due to difficulty of travel and time constraints. This may lead to lower compliance for utilization of S-1 oral treatments.

Auricular point acupressure (APA) is a well-established treatment strategy in traditional Chinese medicine [10]. APA differs from acupuncture in that it requires neither needle insertion nor frequent visits to the therapist's office [11]. Instead, APA works by fixing small plant seeds to the inner or outer auricular surfaces with tiny adhesive patches to stimulate acupoints [10, 11]. The APA technique originated from ancient China and was further studied by Nogier in the 20th century [12]. APA has been recognized by the World Health Organization to have whole-body therapeutic effects [13]. Currently, APA is widely applied to relieve various health problems, including anxiety, pain, smoking cessation, substance abuse, insomnia, nausea and vomiting from pregnancy or chemotherapy, weight control, and low back pain [11]. APA was found to mitigate chemotherapy-induced nausea and vomiting in ten pediatric patients studied for seven days [14].

In this study, we explored the efficacy of APA as a technique to control gastrointestinal dysfunction and improve nutritional status in gastric cancer patients on an at-home oral S-1 therapeutic protocol.

Materials and methods

This was a prospective, randomized, controlled, single-blinded study, which was conducted in accordance with the Declarations of Helsinki. The study was approved by the Ethics Committee of Changhai Hospital. All participants signed informed consent documents.

Patients

Gastric cancer patients were recruited for this study if they met the following criteria: aged 18 years or older and received adjuvant SOX chemotherapy after curative gastrectomy. The exclusion criteria were as follows: additional malignant tumors, auricle defects or infections, previously diagnosed gastrointestinal disorders or having received any acupuncture or acupressure treatments in the past three months.

Intervention

The recruited participants were randomized into two sub-cohorts (control and experimental) by applying restricted randomization methods to achieve a balanced size between the groups. The adjuvant SOX regimens were administered for all patients in three-week cycles. Patients received two-hour intravenous infusions of oxaliplatin (130 mg/m^2) on day one and oral S-1 (40 mg/m^2) twice per day on days 1-14, followed by a rest period for seven days. Patients in the control sub-cohort received non-digestive-organ directed APA treatments, while participants in the experimental sub-cohort had standard APA treatments. Prior to seed fixation, patients were asked to sit comfortably and silently. Outer ears were cleaned with 75% alcohol swabs. Specific auricular points for nausea, vomiting and diarrhea, as defined by Huang *et al.*, were selected in the experimental sub-cohort, including the shenmen, cardia, stomach, sympathetic, digestive subcortex, liver and spleen (**Figure 1A**) [15]. Auricular points selected in the control sub-cohort were not associated with digestive system organs; these points included the eye, wrist, toe and external genitals (**Figure 1B**). The seeds were administered on the first day of a chemotherapy cycle and maintained for 21 days. If the fixations of the seeds were loosened or the seeds were lost, patients were asked to visit the treatment pro-

Table 1. National Cancer Institute common toxicity criteria

Adverse event	Grade				
	0	1	2	3	4
Nausea	None	Able to eat	Oral intake significantly decreased	No significant intake, requiring IV fluids	-
Vomiting	None	1 episode in 24 hours after treatment	2-5 episodes in 24 hours after treatment	≥ 6 episodes in 24 hours after treatment; or need for IV fluids	Requiring parenteral nutrition; or physiologicconsequences requiring intensive care; hemodynamic collapse
Diarrhea	None	Increase of <4 stools/day after treatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or hemodynamic collapse

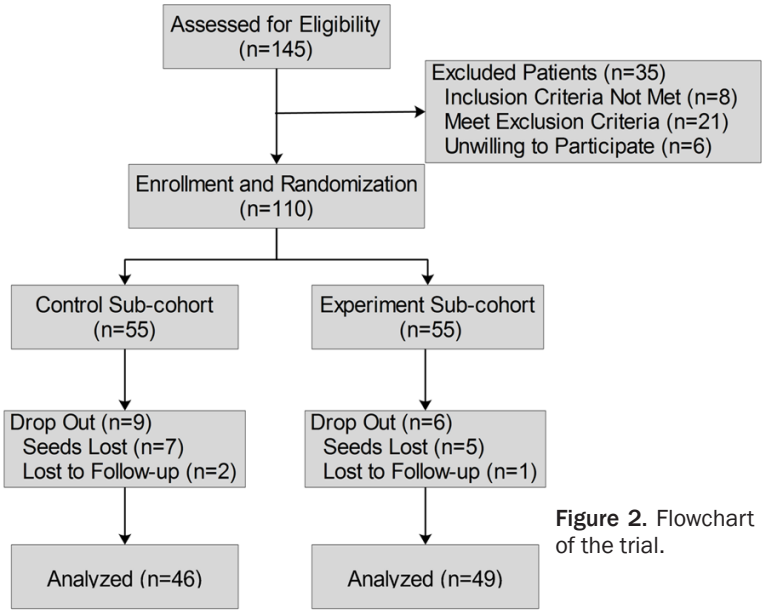

Figure 2. Flowchart of the trial.

vider for re-treatment. Additionally, participants were trained to stimulate the acupoints at least three times per day for at least three minutes each time, even if symptoms were not present.

Measurements

The clinical characteristics of participants were obtained from patient medical records. National Cancer Institute (NCI) common toxicity criteria (version 2.0) guidelines were applied to evaluate the severity of nausea, vomiting and diarrhea (**Table 1**). Participants were taught to record the severity of the adverse events daily throughout the experimental course. Additionally, patients were called every seven days to remind them to answer the questionnaire. The weight, height, total blood protein and albumin levels of each participant were measured two times, at the beginning and end of the study. Body mass index (BMI) was calculated using the following equation: BMI = weight (kg)/height $(m)^2$.

Sample size calculation

The primary study outcome was the difference in vomiting incidence rate between the sub-cohorts. The study was designed to have a statistical power of 0.9 to detect a difference between the sub-cohorts, on the basis of a published vomiting incidence rate of 10% in an experimental sub-cohort and of 40% in controls, with a two-sided alpha value of 0.05 [14, 16]. Achieving these specifications required the recruitment of 40 participants per sub-cohort; 55 patients were recruited per sub-cohort to account for loss-to-follow up.

Statistical analyses

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Comparisons between sub-cohorts were conducted by applying *t*-tests for continuous data and Chi-square tests or Mann-Whitney U tests for categorical data. Given that severities of nausea, vomiting and diarrhea were measured for a 21-day time course, differences between the sub-cohorts were compared using generalized linear mixed modeling methods. A two-tailed $p<0.05$ was considered to be statistically significant.

Results

Patient demographics and clinical data

A total of 145 patients were screened for inclusion in this study. Thirty-five patients were excluded as they did not meet the inclusion criteria, exhibited exclusion criteria or were unwill-

Table 2. Clinical parameters of the enrolled subjects

Characteristics	Control (n = 46)	Experiment (n = 49)	*t* or X^2 value	*p*
Age (years)	61.8±10.0	61.1±9.7	0.204	0.839
Gender				
Male	30 (65.2%)	31 (63.3%)	0.039	0.844
Female	16 (34.8%)	18 (36.7%)		
BMI	23.69±2.07	23.26±2.26	0.995	0.322
Ever smoked	23 (50%)	27 (55.1%)	0.248	0.683
Ever consumed alcohol	34 (73.9%)	32 (65.3%)	0.829	0.383
Invasion depth			0.972	0.808
T1	9 (19.6%)	9 (18.4%)		
T2	12 (26.1%)	11 (22.5%)		
T3	22 (47.8%)	23 (46.9%)		
T4	3 (6.5%)	6 (12.2%)		
Regional lymph node metastasis			0.188	0.980
N0	9 (19.6%)	9 (18.4%)		
N1	15 (32.6%)	16 (32.6%)		
N2	15 (32.6%)	15 (30.6%)		
N3	7 (15.2%)	9 (18.4%)		
Distant metastasis				
Negative	46 (100%)	49 (100%)		
Positive	0	0		
Tumor stage			1.354	0.508
I	1 (2.2%)	2 (4.1%)		
II	21 (45.7%)	27 (55.1%)		
III	24 (52.1%)	20 (40.8%)		
Tumor size (cm)	4.85±2.02	5.35±1.88	-1.236	0.220

Table 3. Incidence, severity and duration of nausea, vomiting and diarrhea

Characteristics	Control (n = 46)	Experiment (n = 49)	*t*, X^2 or Z value	p
Nausea				
Incidence	25 (54.3%)	24 (49.0%)	0.274	0.683
Severity				<0.001
Days (median and range)	12 (2, 21)	8.5 (1, 21)	-2.342	0.019
Days (grade ≥ 2) (median and range)	7 (0, 21)	3 (0, 21)	-2.117	0.034
Vomiting				
Incidence	11 (23.9%)	9 (18.4%)	0.439	0.617
Severity				<0.001
Days (median and range)	10 (5, 16)	6 (3, 9)	-2.062	0.038
Days (grade ≥ 2) (median and range)	5 (0, 16)	2 (0, 5)	-2.067	0.038
Drug request	5 (10.9%)	1 (2.0%)	3.126	0.104
Diarrhea				
Incidence	19 (39.1%)	16 (32.7%)	0.763	0.403
Severity				<0.001
Days (median and range)	8 (3, 21)	5 (2, 16)	-2.316	0.020
Days (grade ≥ 2) (median and range)	3 (0, 21)	0 (0, 5)	-2.559	0.012
Drug requested	9 (19.6%)	2 (4.1%)	5.556	0.025

ing to participate. The final overall cohort consisted of 110 patients randomized at a 1:1 ratio into the control and experimental cohorts, with a sample size of 55 patients each. Nine patients in the control sub-cohort and six patients in the experimental sub-cohort were lost to follow-up. Forty-six and 49 patients with complete data were available in the control and experiment sub-cohorts, respectively (**Figure 2**). No significant differences were found between demographical characteristics of the sub-cohorts, including age, gender, BMI, smoking history, alcohol consumption history, invasion depth, regional lymph node metastasis, distant metastasis, tumor stage and tumor size ($p>0.05$, **Table 2**).

Effects of APA on nausea, vomiting and diarrhea

This study revealed that at the number of patients experiencing nausea throughout the chemotherapy cycles were similar between the two sub-cohorts (25 versus 24, $p = 0.683$, **Table 3**). During the trial, the percent of patients who suffered nausea was higher in the control sub-cohort when compared to patients in the experimental sub-cohort (**Figure 3A**). Furthermore, patients in the control group suffered more intense bouts of

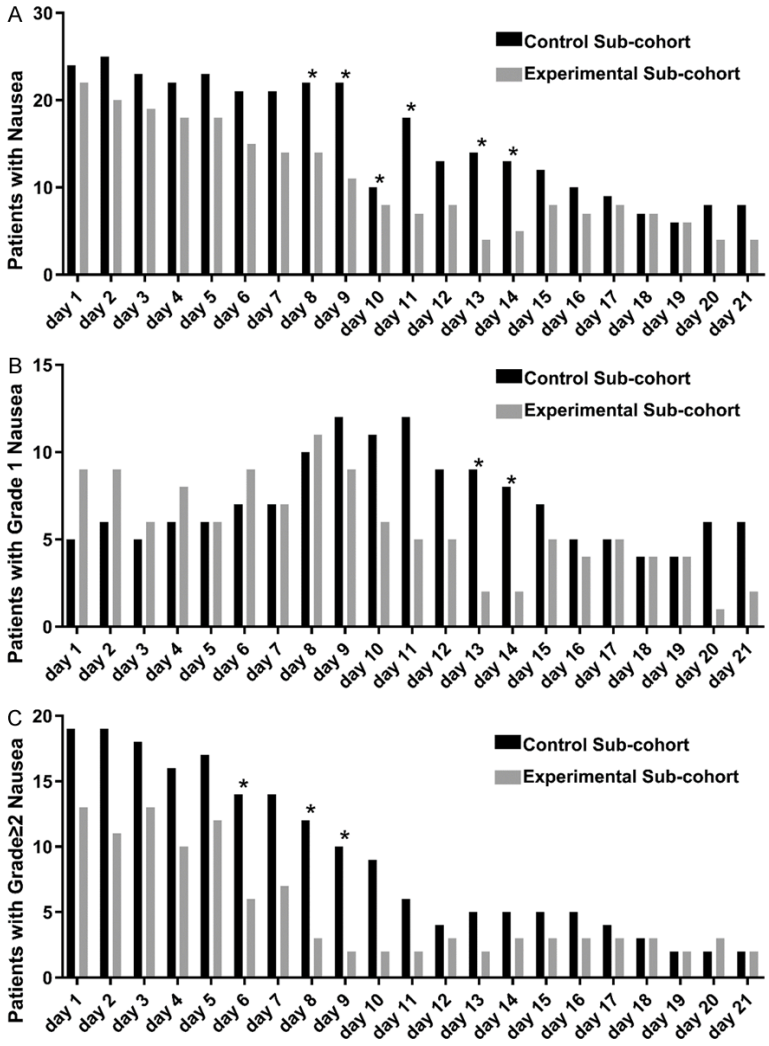

Figure 3. Occurrences of nausea (A), grade 1 nausea (B) and at least grade 2 nausea (C) each day after S-1 was administered. *p<0.05.

nausea than those in the experiment group (p<0.001). Data presented in **Figure 3B** show similar incidence rates of grade 1 nausea between the sub-cohorts, while more patients in the control sub-cohort suffered from ≥ grade 2 nausea events than those in the experiment sub-cohort (**Figure 3C**). Additionally, the durations were longer in the control sub-cohort for both all-grade nausea and ≥ grade 2 nausea adverse events (p = 0.019 and p = 0.034, respectively).

Similar incidence of vomiting between the two sub-cohorts was observed (11 vs 9, p = 0.617, **Table 3**). Data presented in **Figure 4A** show that fewer participants in the experiment sub-cohort experienced vomiting each day. Vomiting was more severe in the control sub-cohort compared to the experimental sub-cohort (p<0.001, **Table 3**). While more participants in the experimental sub-cohort suffered from grade 1 vomiting within the first 5 days of the cycle, as the cycle continued, the number of control patients with grade 1 vomiting surpassed the experimental patients. Additionally, more patients with ≥ grade 2 vomiting were observed in the control group throughout the experimental time course (**Figure 4C**). The duration of all-grade and ≥ grade 2 vomiting was shorter in the experimental sub-cohort when compared to controls (p = 0.038 and p = 0.038, respectively). Five patients in the control sub-cohort required antiemetic drugs, compared to just one patient in the experimental sub-cohort.

Trends in chemotherapy-induced diarrhea reflected those observed for nausea and vomiting. There was no significant difference in the numbers of participants experiencing diarrhea throughout the chemotherapy cycle (19 vs 16, p = 0.403). However, diarrhea was observed more frequently in patients in the control sub-cohort when evaluated per day (**Figure 5A**). Diarrhea adverse events were significantly more serious in the controls (p< 0.001). The number of patients suffering from grade 1 diarrhea were similar between the control and experimental sub-cohorts (**Figure 5B**). More patients in the control sub-cohort experienced ≥ grade 2 diarrhea events (**Figure 5C**). Significant differences were observed between sub-cohorts for duration of both all-grade and ≥ grade 2 diarrhea (p = 0.020 and, p = 0.012, respectively). Additionally, more patients in the control group required medicine to alleviate diarrhea symptoms (9 vs 2, p = 0.025, **Table 3**).

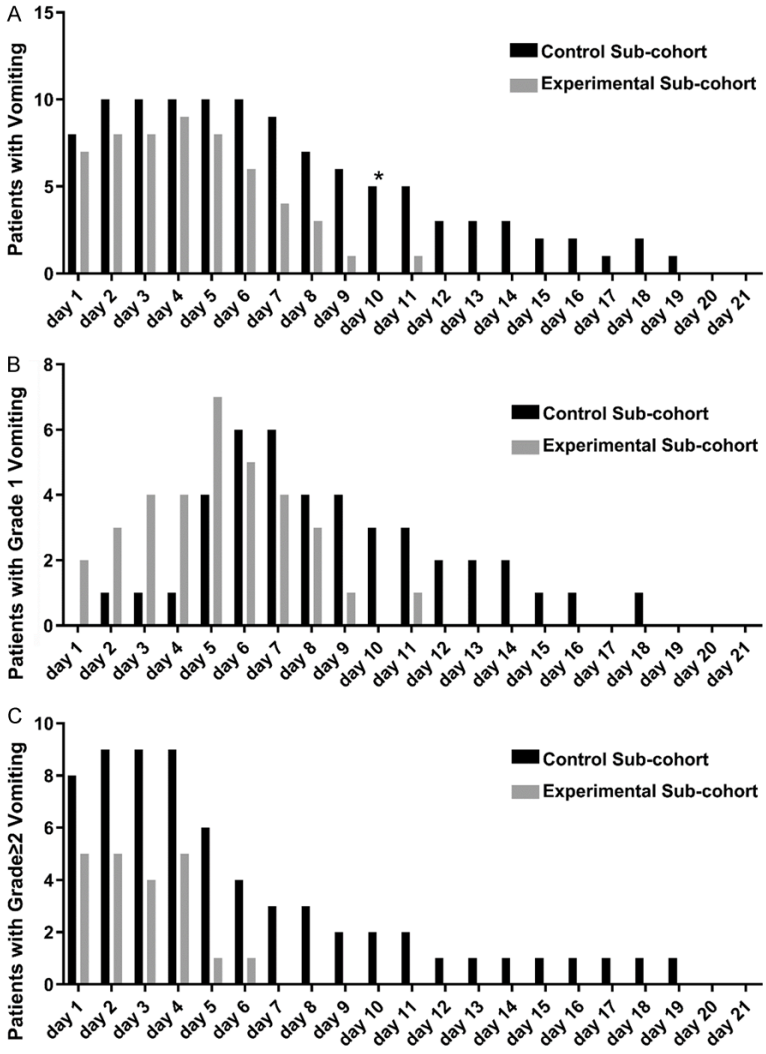

Figure 4. Occurrences of vomiting (A), grade 1 vomiting (B) and at least grade 2 vomiting (C) each day after S-1 was administered. *$p<0.05$.

Effects of APA on nutritional status

Patients were sub-divided by incidence of specific adverse events and then evaluated for nutritional status. Significant differences in weight loss were observed between control and experimental sub-cohorts of patients who experienced vomiting and diarrhea (p = 0.032 and p = 0.032, respectively). These findings were not reflected when evaluating the entire patient population or stratifying by patients who experienced nausea (p = 0.052 and p = 0.070, respectively). BMI also significantly decreased in the control patients who experienced vomiting and diarrhea (p = 0.047 and p = 0.045, respectively). Participants in the experimental sub-cohort experienced less total protein loss both across the entire sub-cohort and when the sub-cohorts were stratified by patients experiencing diarrhea (p = 0.018 and p = 0.007). Altered loss of protein was not observed between control and experimental subpopulations who experienced nausea and vomiting (p = 0.073 and p = 0.122, respectively). Furthermore, significant differences in albumin levels were observed between the control and experimental groups when evaluating both the entire population and when stratifying the sub-cohorts by patients who experienced vomiting and diarrhea (p = 0.002, p = 0.008 and p = 0.017, respectively; **Table 4**).

Discussion

The present study indicated that APA did not significantly reduce the incidence rates of nausea, vomiting and diarrhea in patients receiving oral S-1 therapy, but APA did reduce the severity and duration of these symptoms. Accompanied by the alleviation of these symptoms, patients receiving APA experienced improvements in weight loss and BMI, as well as losses of total protein and albumin levels.

In a previous study, Yeh *et al.* assessed the effects of APA on nausea and vomiting in pediatric patients receiving chemotherapy. The group reported that there were no significant differences between actual APA and sham APA for the prevention and treatment of chemotherapy-induced nausea and vomiting [14]. However, this group did observe a trend towards lowered incidence rates of these adverse events in the APA sub-cohort, along with improved control of nausea and vomiting. This study was limited by a small sample size (10 patients) and short observation period (7 days)

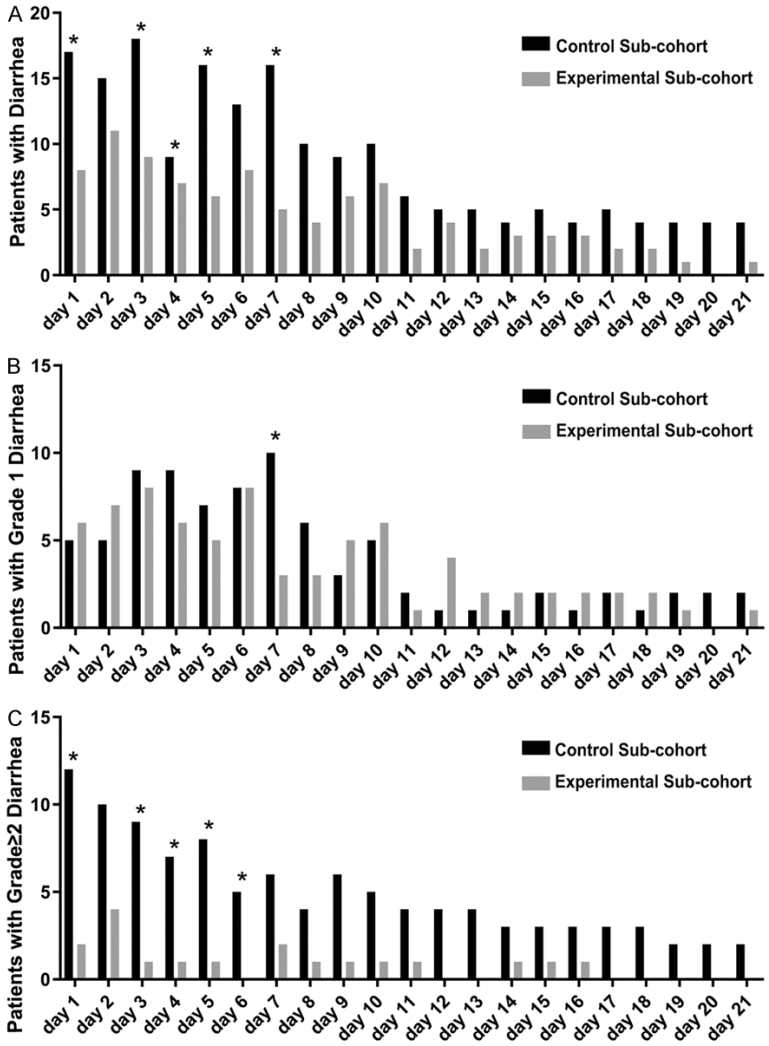

Figure 5. Occurrences of diarrhea (A), grade 1 diarrhea (B) and at least grade 2 diarrhea (C) each day after S-1 was administered. *p<0.05.

[14]. In the present study, trends suggested reductions in nausea, vomiting and diarrhea incidences in the APA sub-cohort; these data were not significantly different between the sub-cohorts. These non-significant findings could be due to inefficacy of APA, limited sample size, or other confounding factors. Larger, randomized, controlled and double-blinded studies are needed to confirm the observed trends.

Given that APA therapy has acupoint specificity [17], the effectiveness of APA for treatment of chemotherapy-induced nausea, vomiting, diarrhea and subsequent nutritional status depends on the selection of specific acupoints. In this study, gastrointestinal tract-related acupoints were selected, including the shenmen, cardia, stomach, sympathetic, digestive subcortex, liver and spleen. These acupoints have been widely used to treat gastrointestinal dysfunctions in China, as reported in previous studies [14]. To avoid biases, control acupoints were also selected. Appropriate control acupoints required no evidence of correlation with the gastrointestinal tract; acupoints targeting the eye, wrist, toe, and external genitals were selected. While participants were asked to stimulate the seeds according a standard protocol, participants may have failed to strictly comply with this step. Additionally, the pressure used during at-home seed stimulation was not standardized. These limitations could have biased the results. Additionally, while Huang *et al.* recommended an APA treatment cycle of five days of continuous followed by two days of rest [15], in this study, the seeds were conserved for 21 days to increase the feasibility by limiting the frequency of visits to the therapist. Participants only visited the therapist when the seeds were loosened or lost. Additionally, previous studies have illustrated recall biases that are introduced when participants completed daily diaries [18-20]. Time-of-day for questionnaire completion was difficult to control or evaluate *post hoc*. This barrier might be overcome in the future by using internet-based questionnaires [21].

APA is a tolerable and widely accepted medical intervention, with frequently reported adverse events limited to discomfort, itching, and ear pain [10, 21-23]. These symptoms were also observed in the present research, but no patients exited the study due to treatment-emergent adverse events. Additionally, allergic reactions to the adhesive material have been

Table 4. Nutrition status change among different subcohorts

Characteristics	Control	Experiment	*t* value	*p*
All patients				
Weight change	-2.43±3.25	-1.10±3.29	-1.972	0.052
BMI change	-0.81±1.07	-0.38±1.16	-1.865	0.065
Total protein change	-5.80±5.42	-2.71±6.91	-2.413	0.018
Albumin change	-4.37±3.87	-1.43±4.94	-3.213	0.002
Nausea patients				
Weight change	-2.24±3.16	-0.55±3.23	-1.851	0.070
BMI change	-0.75±1.05	-0.21±1.13	-1.709	0.093
Total protein change	-6.84±4.58	-4.25±5.29	-1.834	0.073
Albumin change	-4.80±3.08	-3.26±3.25	-1.704	0.095
Vomiting patients				
Weight change	-3.12±2.50	-0.80±1.83	-2.324	0.032
BMI change	-0.98±0.86	-0.24±0.63	-2.121	0.047
Total protein change	-8.64±3.98	-5.00±6.02	-1.621	0.122
Albumin change	-6.36±2.69	-2.44±3.17	-2.993	0.008
Diarrhea patients				
Weight change	-3.14±3.44	-0.44±3.72	-2.238	0.032
BMI change	-1.04±1.11	-0.19±1.31	-2.081	0.045
Total protein change	-6.95±3.24	-2.44±5.91	-2.860	0.007
Albumin change	-6.11±3.30	-2.88±4.30	-2.513	0.017

reported in other studies [21, 22] but were not observed here. While the effects of potential APA-emergent adverse events are considered minimal, these symptoms were emphasized in the consenting process.

As illustrated in previous studies [22, 24], the cost of APA is relatively low. Thus, use of this technique will not place a heavy economic burden on the patients or the medical health insurance fund. Another advantage of APA is that after a single visit to a therapist for seed fixation, participants can stimulate the acupoints themselves with home care. Once applied, seeds can be maintained for two to four weeks [11]. In the present study, the seeds were maintained for 21 days, and only a small proportion of patients required additional therapist visits. In contrast, patients receiving acupuncture treatments for the same symptoms require frequent therapist visits. Previous studies have indicated that acupuncture does not reduce medical costs for the control of chronic lower back pain when compared with therapeutic massage and self-care education [25].

While elucidation of the mechanistic underpinnings of APA could facilitate acceptance of the technique, these data remain unclear. Research investigating traditional Chinese medicine found that correlations exist between the ear and other regions of the human body and that all meridians have reference points on the ear [26]. Stimulation of acupoints in the ear may regulate the function of other organs through meridians. Additionally, in 1950, Nogier *et al.* published a theory that the ear represents the inverted fetus within the womb; this has also been accepted by most traditional Chinese medical doctors [27, 28]. Understanding definitive physiological mechanisms of APA will require more research. This study found that for chemotherapy-induced digestive side effects, APA targeting gastrointestinal-targeted acupoints was more effective than APA targeted to other non-gastrointestinal acupoints. These data suggest that therapeutic effects of APA are acupoint-specific.

Although the results of the study were encouraging, several limitations should be considered. First, all subjects were enrolled from a single center, thus limiting the generalizability of the results. Second, no statistically significant difference was observed in the primary study outcome (incidence of vomiting rates), which may be due to the limited sample size or lack of APA efficacy. However, given that targeted APA improved both duration and severity of chemotherapy-induced adverse events, it is recommended to perform a larger multi-center study to confirm these results. Third, the study was single-blind study, which reduced the strength of the data. Fourth, a control group that was not treated with APA (either on-target or off-target) was not included. Finally, the mechanistic underpinnings of APA were not evaluated in this study. Future studies will focus on this topic.

Conclusion

APA treatment is a feasible technique to decrease the severity and duration of nausea, vomiting and diarrhea events experienced by gastric cancer patients receiving S-1 therapy. Use of this technique may have improved the nutritional status of recipients. These data did

not indicate that gastrointestinal-targeted APA reduced overall incidence rates of nausea, vomiting and diarrhea. More studies are needed to verify the findings of the present research and to further explore the underlying mechanisms of APA.

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Disclosure of conflict of interest

None.

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References

[1] Huang YK and Yu JC. Circulating microRNAs and long non-coding RNAs in gastric cancer diagnosis: an update and review. World J Gastroenterol 2015; 21: 9863-9886.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.

[3] Gunderson LL. Gastric cancer--patterns of relapse after surgical resection. Semin Radiat Oncol 2002; 12: 150-161.

[4] Gallo A and Cha C. Updates on esophageal and gastric cancers. World J Gastroenterol 2006; 12: 3237-3242.

[5] Earle CC and Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999; 35: 1059-1064.

[6] Yang L, Yang Y, Qin Q, Zhou A, Zhao J, Wang J, Shu C, Yuan X and Hu S. Evaluation of the optimal dosage of S-1 in adjuvant SOX chemotherapy for gastric cancer. Oncol Lett 2015; 9: 1451-1457.

[7] Kilic L, Ordu C, Yildiz I, Sen F, Keskin S, Ciftci R and Pilanci KN. Current adjuvant treatment modalities for gastric cancer: from history to the future. World J Gastrointest Oncol 2016; 8: 439-449.

[8] Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm I, Lugauer S, Behrens C, Weiberlenn T, Hasan C, Gottschling S, Wild-Bergner T, Henze G and Driever PH. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology. Interim results of a multicenter crossover study. Support Care Cancer 2006; 14: 172-176.

[9] Herr I, Ucur E, Herzer K, Okouoyo S, Ridder R, Krammer PH, von Knebel Doeberitz M and Debatin KM. Glucocorticoid cotreatment induces apoptosis resistance toward cancer therapy in carcinomas. Cancer Res 2003; 63: 3112-3120.

[10] Yeh CH, Chien LC, Lin WC, Bovbjerg DH and van Londen GJ. Pilot randomized controlled trial of auricular point acupressure to manage symptom clusters of pain, fatigue, and disturbed sleep in breast cancer patients. Cancer Nurs 2016; 39: 402-410.

[11] Yeh CH, Chien LC, Huang LC and Suen LK. Auricular point acupressure for chronic pain: a feasibility study of a 4-week treatment protocol. Holist Nurs Pract 2014; 28: 184-194.

[12] Nogier P. Handbook to auriculotherapy. france: maisonneuve: 1981.

[13] World Health Organization. WHO report of the working group on auricular nomenclature. Lyons, France: World Health Organization, 1990.

[14] Yeh CH, Chien LC, Chiang YC, Lin SW, Huang CK and Ren D. Reduction in nausea and vomiting in children undergoing cancer chemotherapy by either appropriate or sham auricular acupuncture points with standard care. J Altern Complement Med 2012; 18: 334-340.

[15] Huang LC and Huang WS. Handbook of auricular treatment prescriptions & formulae. Orlando, FL: Auricular International Research & Training: 2007: 310.

[16] Hong YS, Park YS, Lim HY, Lee J, Kim TW, Kim KP, Kim SY, Baek JY, Kim JH, Lee KW, Chung IJ, Cho SH, Lee KH, Shin SJ, Kang HJ, Shin DB, Jo SJ and Lee JW. S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial. Lancet Oncol 2012; 13: 1125-1132.

[17] Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for low back pain: a systematic review. Spine 2008; 33: E887-E900.

[18] Sorbi MJ, Peters ML, Kruise DA, Maas CJ, Kerssens JJ, Verhaak PF and Bensing JM. Electronic momentary assessment in chronic pain I: psychological pain responses as predictors of pain intensity. Clin J Pain 2006; 22: 55-66.

[19] Stone AA, Shiffman S, Schwartz JE, Broderick JE and Hufford MR. Patient compliance with paper and electronic diaries. Control Clin Trials 2003; 24: 182-199.

[20] Schneider S, Stone AA, Schwartz JE and Broderick JE. Peak and end effects in patients' daily recall of pain and fatigue: a within-subjects analysis. J Pain 2011; 12: 228-235.

[21] Yeh CH, Kwai-Ping Suen L, Chien LC, Margolis L, Liang Z, Glick RM and Morone NE. Day-to-

day changes of auricular point acupressure to manage chronic low back pain: a 29-day randomized controlled study. Pain Med 2015; 16: 1857-1869.

[22] Yeh CH, Chien LC, Chiang YC and Huang LC. Auricular point acupressure for chronic low back pain: a feasibility study for 1-week treatment. Evid Based Complement Alternat Med 2012; 2012: 383257.

[23] Yeh CH, Morone NE, Chien LC, Cao Y, Lu H, Shen J, Margolis L, Bhatnagar S, Hoffman S, Liang Z, Glick RM and Suen LK. Auricular point acupressure to manage chronic low back pain in older adults: a randomized controlled pilot study. Evid Based Complement Alternat Med 2014; 2014: 375173.

[24] Yeh CH, Chien LC, Chiang YC, Ren D and Suen LK. Auricular point acupressure as an adjunct analgesic treatment for cancer patients: a feasibility study. Pain Manag Nurs 2015; 16: 285-293.

[25] Cherkin DC, Eisenberg D, Sherman KJ, Barlow W, Kaptchuk TJ, Street J and Deyo RA. Randomized trial comparing traditional Chinese medical acupuncture, therapeutic massage, and self-care education for chronic low back pain. Arch Intern Med 2001; 161: 1081-1088.

[26] Yeh CH, Chien LC, Balaban D, Sponberg R, Primavera J, Morone NE, Glick R, Albers KM, Cohen SM, Ren D, Huang LC and Suen LK. A randomized clinical trial of auricular point acupressure for chronic low back pain: a feasibility study. Evid Based Complement Alternat Med 2013; 2013: 196978.

[27] Huang LC. Auricular medicine: a complete manual of auricular diagnosis and treatment, auricular international research & training. Orlando, Fla, USA: 2005.

[28] Oleson T. Auriculotherapy manual: Chinese and western systems of ear acupuncture, 3rd edition. Churchill Livingstone, London, UK: 2003.