ORIGINAL ARTICLE

Auricular acupressure: reducing side effects of chemotherapy in women with ovarian cancer

Ying Tsao[1] · Debra K. Creedy[2]

Abstract

Purpose Many women with ovarian cancer may experience adverse effects from adjuvant chemotherapy after surgery. Non-pharmacological interventions can be used to reduce these side effects. We tested auricular acupressure to reduce treatment side effects in this population.

Methods A prospective, quasi-randomized controlled trial was carried out at a publicly-funded hospital in southern Taiwan. Thirty-four women in the intervention group received auricular acupressure at four points (Shenmen, subcortex, endocrine, and heart), three times per day for 3 min per time, for 6 weeks. Thirty-one women in the control group received routine nursing care alone. The M. D. Anderson Symptom Inventory (MDASI) was completed at four time points.

Results After receiving the third cycle of chemotherapy, side effect severity was elevated among both groups. Auricular acupressure reduced side effects such as disturbed sleep ($t = -11.99$; $p < .001$, eta squared $= 0.69$), fatigue ($t = -2.57$; $p < .01$, eta squared $= 0.10$), and lack of appetite ($t = -2.37$; $p = .024$, eta squared $= 0.08$).

Conclusion Auricular acupressure can reduce adverse side effects of chemotherapy in women with ovarian cancer. Future studies with a larger sample and using some laboratory-based tests (such as C-reactive protein, interleukin-6) are warranted to confirm the results.

Keywords Auricular acupressure · Chemotherapy · Ovarian cancer · Side effect management · Women

Introduction

Around 22,440 women in the USA are diagnosed with ovarian cancer each year [1]. In developed Asian countries such as Taiwan, the age-standardized incidence rates of ovarian cancer have increased since 2002 (348.39 per 100,000) to 2012 (401.18 per 100,000) [2]. About 70% of all ovarian cancer patients are diagnosed at an advanced-stage (International Federation of Gynecology and Obstetrics; FIGO Stage III and IV), at which time more intensive treatment may be required to control clinical signs and prevent progression of this disease [3].

Patients undergoing treatment typically suffer multiple side effects simultaneously. This phenomenon known as a "symptom cluster" is defined as "two or more concurrent symptoms/side effects that occur together with a high degree of predictability" [4]. Etiology of a symptom cluster may be elusive when side effects stem from combination treatments or the cancer itself [5]. Women with cancer are more likely to experience unique symptom clusters associated with the reproductive organs, such as abdominal discomfort or pelvic pain [6]. The presence of debilitating symptoms from cancer and its treatment is extremely concerning because of the adverse impact on clinical outcomes and patients' quality of life [7].

Management of treatment side effects and improving outcomes for cancer patients are a crucial part of nursing care. The effectiveness and safety of pharmacological and non-pharmacological interventions to alleviate side effects have been carefully examined. According to a recent Cochrane Review of 45 randomized controlled trials (RCTs) with 4696 participants, there was insufficient evidence to support the use of prescription medication (such as amantadine, modafinil,

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and methylphenidate) to treat cancer-related fatigue [8]. In contrast, a systematic review of 11 RCTs showed that complex nursing interventions (including patient education, symptom assessment, counseling, and coaching) produced clinically important reductions in chemotherapy-related burden of side effects by 10–88% [9]. However, there is relatively little research regarding the efficacy of traditional Chinese medicine (TCM) on reduction of side effects in patients with cancer, compared to mainstream treatments. A recent meta-analysis of 13 RCTs involving 806 participants found that auricular therapy for pain management in patients with cancer or chronic disease was effective compared to routine care [10]. The overall standardized mean difference (SMD) was 1.59 (95% CI − 2.36, − 0.82). Similarly, a meta-analysis pooled 40 RCTs that used acupressure, reflexology, or auricular acupressure for insomnia in any patient group and found that auricular acupressure was more effective than no intervention or usual care [11]. Overall, however, there is a lack of evidence on the impact of auricular acupressure interventions on symptom clusters in women with ovarian cancer undergoing chemotherapy. The aim of the current study was to examine the efficacy of a 6-week auricular acupressure intervention on reducing treatment side effects among women with ovarian cancer.

Background

According to TCM, several distinct symptom clusters are primarily due to a dysfunction between organ systems, an imbalance between *Yin* and *Yang*, and a disharmony in the flow *Qi* and blood [12]. "Acupuncture" is defined as the stimulation of a special point on the body by a specific method (such as needles, electric stimulation, and auricular acupressure) to achieve a therapeutic or homeostatic effect (returning the body to its normal state). The special anatomical point on the body is called "Shu Xu" or acupuncture point (acupoint) [13].

Auricular acupuncture can be done manually (known as acupressure), with an acupuncture needle, a laser, magnets, or ear seeds. These methods can be used as complementary treatments and generally contribute to improved symptoms and reduced exacerbations [14]. A quality RCT with 90 cancer patients found auricular acupuncture (involving needles) for 8 weeks significantly reduced pain intensity measured by visual analog scores [15].

Just like acupuncture with filiform needles, auricular acupressure stimulates specific acupoints on the external ear to improve well-being. Auricular acupressure is relatively convenient to apply, and does not require a patient to disrobe [14]. Compared to pharmaceutical treatment, auricular acupressure for 7 days had a positive effect (30% reduction in scores) on pain, fatigue, and disturbed sleep among breast cancer patients [16]. A recent pilot RCT by Kuo et al. [17] found that compared to controls, women (n = 20) undergoing chemotherapy

for ovarian cancer reported improved sleep following a 6-week course of auricular acupressure and information on sleep hygiene practices.

In the review by Yeung et al. [11], 16 of the 40 studies used auricular acupressure stimulation. Of these, 13 studies commonly stimulated the Shenmen, heart, occipital, subcortex, endocrine, liver, and kidney areas using semen vaccaria seeds and pellets. Generally, ear acupoints were pressed around 3 times a day, and pellets were changed 3.1 times per week for an average of 3 to 4 weeks (26.5 days) [11].

Auricular acupressure may provide a mechanism to treat multiple side effects of cancer treatment with one modality, thereby limiting the risk of polypharmacy, which can occur when treating side effects individually [18]. Some auricular points may treat multiple symptoms and side effects. For instance, the "Shenmen (TF4)" point is often considered to be a primary point for pain reduction. TF4 is also considered to alleviate apprehension, fear, anxiety, and help regulate the sympathetic nervous system [19]. The "subcortex (AT4)" point represents the whole diencephalon and is the highest level of the supra-spinal gate control system. AT4 is used for most pain disorders and also reduces neurasthenia, such as headache, dizziness, fatigue, insomnia, and poor concentration [20]. The "endocrine (CO18)" point achieves appropriate homeostatic levels of endocrine hormones, and has anti-allergic and anti-inflammatory effects [21]. The "heart (CO15)" point can have a depressing and immediate effect on cardiac function [22].

Methods

Study design and participants

A prospective, quasi-randomized controlled trial was performed from January 2017 to June 2018. Participants were recruited from the gynecological ward of a publicly funded hospital located in southern Taiwan. Women were eligible for inclusion if they were 18 years or older, receiving chemotherapy for newly diagnosed ovarian cancer, had no history of sleep, neurologic, or psychiatric disorders, could communicate independently, and willing to comply with study-related procedures. Exclusion criteria included evidence of metastases at the time of diagnosis, cognitive impairment, or allergy to the tape used to affix the auricular acupressure seeds on the outer ear.

Measures

Descriptive variables included participants' demographic characteristics (age, marital status, education level, and religion and alcohol drinking and smoking habits) and medical history (disease diagnosis and treatment status).

Patient-reported side effect severity and interference during the previous 24 h, as measured by the M. D. Anderson Symptom Inventory (MDASI), was the outcome variable. The MDASI contains 13 symptom items (i.e., pain, fatigue, nausea, sleep disturbance, distress, shortness of breath, trouble remembering, loss of appetite, drowsiness, dry mouth, sadness, vomiting, and tingling), and 6 interference items (i.e., general activity, mood, work, relations with others, walking, enjoyment of life). All items are rated on a 0–10 numeric scale, with 0 meaning *not present* and 10 meaning *as bad as you can image*. Symptom burden is the sum of the severity and impact of symptoms associated with cancer or side effects of conventional treatment. Each item on the MDASI can be used individually or in subsets without summary scoring if specified a priori [23, 24]. Based on previous studies, symptom severity was categorized as mild for scores of 3 or less, moderate for scores from 4 to 6, and severe for scores of 7 and over [25, 26].

The MDASI has good reliability and construct validity across ethnically diverse populations [27]. In the Taiwanese sample, the internal consistency Cronbach's alpha of the MDASI was 0.89 for symptom severity and 0.94 for interference items. A subsequent confirmatory factor analysis resulted in a two-factor solution (general and gastrointestinal symptoms) for 13 symptom severity items [28]. The MDASI is rated highly in terms of comprehensibility, readability, ease of completion, and utility in the management of treatment side effects [29]. In our sample, the Cronbach's alpha for the MDASI was 0.92, showing adequate internal consistency.

To evaluate clinically meaningful improvements, we looked at the minimal important difference (MID) of the MDASI. MID is defined as "the smallest difference in scores which participants perceive as beneficial and which would mandate, in the absence of troublesome side effects" [23]. According to Cleeland et al., a difference of 0.98 to 1.21 can provide convincing clinical evidence of a treatment benefit [23]

Procedure

At the participating hospital, surgery is the initial treatment for most women with ovarian cancer followed by chemotherapy. During the first cycle of chemotherapy, clinic staff were briefed about the project and asked to identify potential participants. A researcher then contacted each potential participant to explain the objectives and processes of the study and obtain consent.

All participants completed the MDASI following their first chemotherapy treatment (time 0) and re-evaluated after their third chemotherapy treatment (time 1). Generally, patients with ovarian cancer experience more discomfort after completion of the second round of chemotherapy. At this time, patients may be less motivated to learn new practices or develop new skills, so introduction of the auricular acupressure intervention occurred in the third cycle.

Consecutive patients were recruited and alternatively assigned to the control or intervention group, utilizing quasi-randomization based on day of the week of admission. Women in the control group received routine nursing care, and the intervention group received routine care and auricular acupressure treatment. All participants completed the MDASI after the 5th chemotherapy cycle (time 2; 4-week auricular acupressure intervention), and 6th chemotherapy cycle (time 3; 6-week auricular acupressure intervention).

Auricular acupressure intervention

After the 3rd chemotherapy session and prior to discharge, the first auricular acupressure was conducted by one of three trained research nurses. The patient chose either the left or right auricle (pinna) which was then sterilized with a 75% alcohol solution. The four acupressure points were identified, and the nurse placed a vaccaria seed on each point attached with adhesive tape. Afterwards, the nurse instructed the woman to press each point three times per day for 3 min per time (i.e., morning, noon, and night) [11]. The pressure technique involved constant stimulation through a stable and gradually firmer pressure until a slight discomfort/soreness or tingling sensation was felt. Auricular acupressure alternated from one ear to the other over a period of 3 days. The required number of taped vaccaria seeds was provided free of charge to participants. The research nurses also provided written materials and prompts on how to precisely locate and select acupoints for self-treatment at home. When participants attended their outpatient appointment in the week following chemotherapy, they were contacted by the research nurses about any difficulties performing the acupressure or to answer any questions. While resting at home, participants received phone calls by the research nurses as a reminder to perform the acupressure.

Sample size

In the study, sample size was calculated based on a 1.5-point difference between baseline and post-treatment insomnia as measured by the Pittsburgh Sleep Quality Index (PSQI) using preliminary results from our prior study in women with ovarian cancer [17]. Assuming a 20% drop-out rate, a minimum of 58 participants was necessary to give 80% power and an alpha of 0.05 level to detect any difference between groups [30].

Data analysis

Statistical Package for the Social Sciences (SPSS), version 22, was used for the data analysis. Descriptive statistics, like mean and standard deviation (SD) were calculated for overall symptom burden on the MDASI. Inferential statistics, such as

independent t test (to compare the means of overall MDASI scores between groups), and repeated measures ANOVA with pairwise comparisons were conducted. Bonferroni's correction was applied to post hoc analyses (for comparing means across four time points in both groups as well as to reduce type I error). Chi-square tests were also applied to compare both groups in terms of demographical characteristics. Eta squared values were calculated manually and the magnitude of difference between groups determined using Cohen's d (0.2 = small; 0.5 = moderate; 0.8 = large effect).

Results

Participant recruitment, withdrawal, and retention

Eighty-two women recently diagnosed with ovarian cancer were assessed for participation. Of these, three women had a past history of psychiatric illness (such as depression), and regularly used either antipsychotics, or mood-stabilizing medications. Three other women had existing disturbed sleep or

other health concerns like unexplained anemia and allergies, and were not approached to participate. Two women diagnosed with metastatic ovarian cancer were also excluded.

Seventy-four women met the eligibility criteria. Of these women, nine refused acupressure treatment. The main reason for not participating was reluctance to use the tape with vaccaria seed or provide personal details. Therefore, 65 women provided informed consent and were randomized to the intervention group (A) ($n = 34$) or control group (B) ($n = 31$) at time 0.

During the trial, four women were transferred to other facilities or lost to follow-up. One woman died from ovarian cancer after undergoing her 5th round of chemotherapy. Accordingly, 60 women completed the trial giving a retention rate of 93% (as outlined in Fig. 1).

Participant characteristics

Over half of the participants were married ($n = 34$; 57%). Around half ($n = 38$; 64%) had undertaken education beyond high school. Nearly half of the respondents ($n = 29$, 48%)

Fig. 1 Flowchart of participant recruitment
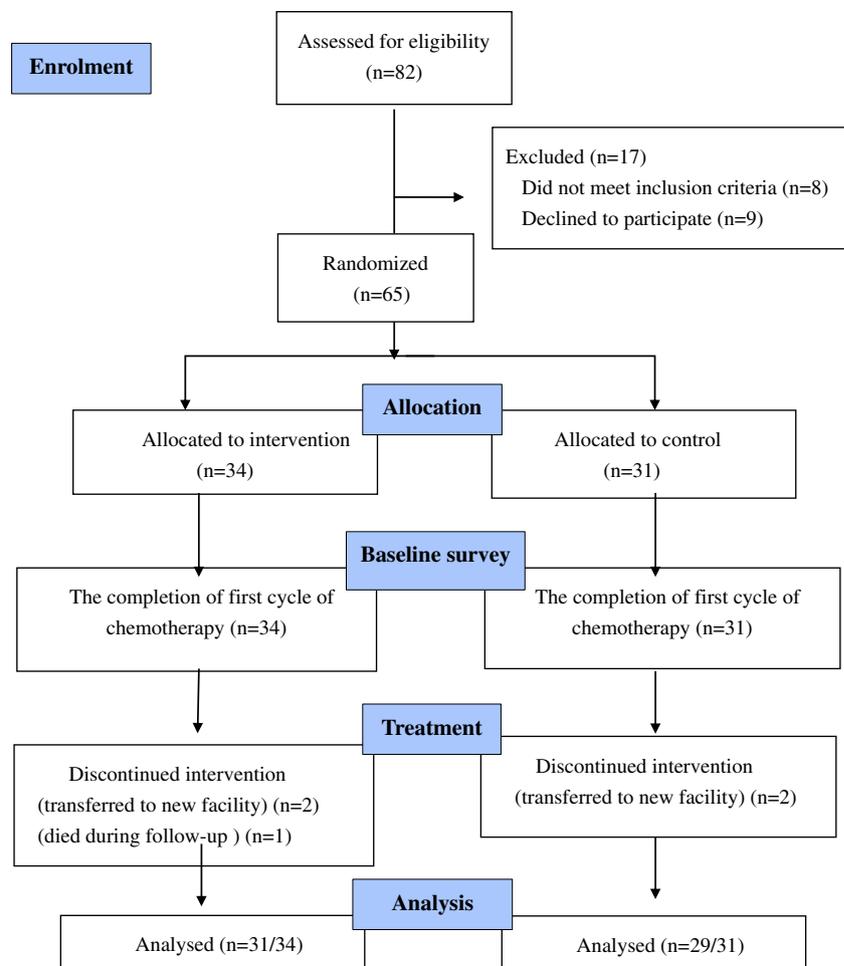
stated that they held Buddhist beliefs, and one quarter stated that they have no religion ($n = 15$, 25%). Over two-thirds ($n = 42$; 70%) of women were diagnosed with stage III ovarian cancer ($n = 7$ stage I, $n = 6$ stage II, $n = 5$ stage IV). Mean age was 53.3 years (SD = 12.4; range 19.8~70.6) for the intervention group and 55.6 years (SD = 13.1; range 26.4~78.2) for the control group. No statistically significant differences were found for demographic characteristics or MDASI scores at baseline (see Table 1).

Outcome measures: burden of side effects

After completion of the first cycle of chemotherapy (time 0), the burden of side effects ranged from 0 to 8.95, with a mean of 2.38 (SD = 1.57). After the third cycle of chemotherapy (time 1), participants reported an increased sense of burden, from an average of 2.38 to 3.45 (SD = 1.59), which is considerable.

Among the women in the control group, the mean MDSAI scores increased from 2.24 (time 0) to 3.71 (time 1) indicating an increase burden following the commencement of chemotherapy.

The mean MDSAI scores tended to increase slightly throughout time 2 (mean = 3.92) and time 3 (mean = 4.05) (Pillai's trace $F = 7.65$, $p = .001$, and partial $\eta^2 = 0.47$). Conversely, mean MDSAI scores of the acupressure group significantly reduced in the period from time 1 (mean = 3.19) to time 2 (mean = 2.50) and time 3 (mean = 2.40) (Pillai's trace $F = 3.45$, $p = .03$, and partial $\eta^2 = 0.27$).

Compared with the control group, the intervention group revealed lower mean scores on MDASI, both at time 2 and time 3. The between-group difference of 1.42 points on the MDASI at time 2, and 1.65 points at time 3, was greater than the defined MID of 1.21 points [23] (see Table 2).

In regard to the component scores of the MDASI, 31 women receiving the auricular acupressure intervention had lower side effect severity scores than they previously reported (time 1). In particular, after 4 weeks of APA (auricular point acupressure; time 2), the scores on four different side effects dropped indicating improvements in: disturbed sleep (− 4.19) ($t = − 10.27$; $p < .001$), fatigue (− 1.04) ($t = − 2.56$; $p = .016$), relations with other people (− 1.0) ($t = − 2.45$; $p = .02$), and enjoyment of life (− .9) ($t = − 2.12$; $p = .041$).

Table 1 Demographic characteristics of participants ($N = 60$)

	Mean (SD) or n (%)				
	Control group ($n_2 = 29$)	Acupressure group ($n_1 = 31$)	F	χ^2	p
Age	55.6 (± 13.1)	53.3 (± 12.4)	0.48		.49
Education				6.72	.24
Elementary school	8	4			
Junior school	4	6			
High school	11	10			
Undergraduate	6	6			
Masters	0	4			
PhD		1			
Marital state				7.24	.12
Single	5	8			
Married	15	19			
Divorced	5	0			
Widowed	4	3			
Separated	0	1			
Religion				5.66	.34
None	7	8			
Buddhism	12	17			
Taoism	6	3			
Christian	4	1			
Other (I-Kuan Tao)	0	2			
Cancer stage				2.70	.43
I	5	2			
II	2	4			
III	18	24			
IV	4	1			

Table 2 Comparisons of means of overall MDSAI scores

Symptom scores (mean ± SD)	Baseline time 0	Time 1	Time 2 4 weeks of acupressure	Time 3 6 weeks of acupressure	A repeated measures ANOVA with post hoc Bonferroni's tests (mean difference (p))					
					Time (1–0)	Time (2–0)	Time (3–0)	Time (2–1)	Time (3–1)	Time (3–2)
Acupressure	2.50 (± 1.42)	3.19 (± 1.24)	2.50 (± 0.98)	2.40 (± 0.97)	.69 (.22)	.004 (1.00)	−.09 (1.00)	−.68* (0.03)	−.79* (0.01)	−.10 (1.00)
Control	2.24 (± 1.73)	3.71 (± 1.88)	3.92 (± 1.90)	4.05 (± 1.74)	1.47* (.002)	1.68* (.003)	1.816* (.001)	.21 (1.00)	.34 (.21)	.13 (1.00)
Independent t test										
(p value)	− .64	1.27	.001*	<.001*						

Time 0: after 1st cycle of chemotherapy; time 1: after 3rd cycle of chemotherapy; time 2: after 5th cycle of chemotherapy; time 3: after 6th cycle of chemotherapy

*$p < .05$

After 6 weeks of auricular acupressure (time 3) side effects continued to decline compared to time 1, especially for disturbed sleep (− 4.54) ($t = − 11.99$; $p < .001$, eta squared = .69) with moderate effect. There was also reduced fatigue (− 1.0) ($t = − 2.57$; $p < .01$, eta squared = .10), improved appetite (− .88) ($t = − 2.37$; $p = .02$, eta squared = .08), general activity (− 1.35) ($t = − 3.33$; $p = .002$ eta squared = .27), mood (− 1.06) ($t = − 2.68$; $p = .02$, eta squared = .10), and enjoyment of life (− 1.03) ($t = − 2.24$; $p = .032$, eta squared = .07) with small effect (see Fig. 2).

Discussion

Diagnosis and treatment of ovarian cancer entails an increased risk for serious treatment side effects in women. One longitudinal survey identified six symptom clusters of side effects (pain-related, psychological, menopausal, gastrointestinal, body image, and peripheral neurological symptom cluster) among 115 Chinese women with ovarian cancer after surgery [31]. Several side effects within the "menopausal symptom cluster" included lack of energy, dry mouth, difficulty sleeping, and lack of appetite. The components of this cluster were relatively stable throughout the trajectory of the disease [31]. The present study revealed that "disturbed sleep" had the highest incidence among study participants. The high incidence of sleep disturbance was also reported by Kuo et al. [17] in their auricular acupressure intervention study. Fatigue (lack of energy or motivation), pain/tingling/numbness (peripheral sensory neuropathy), and appetite changes all showed a high incidence in the current study.

Chemotherapy-induced peripheral neuropathy (CIPN) is common in gynecologic cancer patients receiving taxanes and platinum-based agents and can negatively affect quality of life and everyday functioning [32]. CIPN is characterized by pain, numbness, and tingling, typically located in the hands and feet. Results of a systematic review of 31 RCTs with 4179 participants showed that the overall prevalence of CIPN was the highest within the 1st month after chemotherapy [33]. Approximately, one third of cancer patients can expect to have chronic CIPN for 6 months or more after chemotherapy [33].

Many preventive and treatment strategies for CIPN have been explored without significant efficacy or duration of response [34]. However, techniques such as physical and occupational therapy may help overall functional status in cancer survivors. Recently, other complementary and alternative medicine (CAM) techniques have been recommended to manage patients' cancer-related treatment side effects including acupuncture and other related therapies (acupressure) [35]. Furthermore, a review of self-acupressure that included eight RCTs and two quasi-RCTs [36] reported significant improvements in symptom scores, such as nausea and vomiting, stress/fatigue, and sleep disturbances. Importantly, another review of
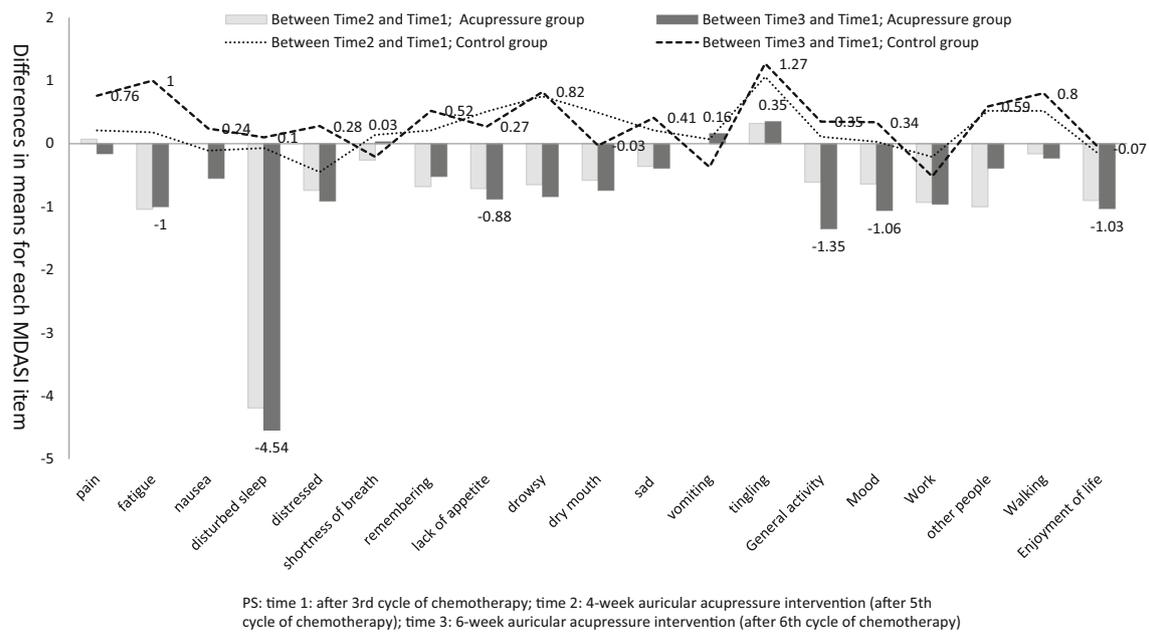
PS: time 1: after 3rd cycle of chemotherapy; time 2: 4-week auricular acupressure intervention (after 5th cycle of chemotherapy); time 3: 6-week auricular acupressure intervention (after 6th cycle of chemotherapy)

Fig. 2 Differences in means for each MDASI item between two time-points (time 1; time 2 or time 3)

43 studies [37] reported that acupressure had no adverse effects in most studies (84%). However, more methodologically rigorous trials are needed for definitive evidence regarding intervention efficacy.

Our study results indicated that after receiving the third cycle of chemotherapy, elevated side effects were observed among both groups, but the 6-week APA intervention significantly reduced side effects (such as disturbed sleep, fatigue, and lack of appetite). Moreover, women receiving acupressure reported significantly lower levels of neuropathic symptoms (such as pain, tingling, and improved general activity) compared with controls. The changed scores indicated clinically significant improvement. These results add to the growing evidence on the efficacy of auricular acupressure in controlling side effects and preventing exacerbations in women with ovarian cancer undergoing chemotherapy. It is also important to note that early assessment and early intervention are key components in successfully reducing cancer-related treatment side effects in this population.

Limitations

The study was conducted in a single hospital with a relatively small number of potential participants, which may restrict the generalizability of our findings. In addition, questionnaires, although inexpensive and practical, are limited in providing a reasonably accurate assessment of the severity and impact of side effects experienced by cancer patients. The outcomes may be limited by recall bias, but it is unlikely that recall would be affected according to case status, such that women in the intervention would recall more severe side effects than women in the control group, and vice-versa.

The effectiveness of auricular acupressure for reducing treatment side effects depends on adherence to the recommended protocol. We failed to track participants' performance of these daily tasks. Nevertheless, all participants were successfully contacted during each outpatient visit or through telephone calls reminding them about the intervention. We suggest that further research could build on the current findings by calculating symptom trajectories from inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) [38].

Conclusions and implications

The current study demonstrated that the 6-week auricular acupressure intervention reduced side effects in women with ovarian cancer undergoing chemotherapy with moderate effect. Auricular acupressure has the advantage of being non-invasive, self-managing, and inexpensive to apply. Conducting auricular acupressure is within the scope of nursing practice following some TCM training, and appears to be a promising approach to help women with ovarian cancer experiencing disturbing side effects. Future studies with larger samples and using some laboratory-based tests are warranted to confirm the results.

Compliance with ethical standards All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee (VGHKS16-CT12–28) and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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