Application of Auricular Acupoint Pressing Combined With Zusanli Acupoint Injection of Vitamin B1 in Patients with Breast Cancer Undergoing Chemotherapy

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Abstract: This study evaluated the clinical efficacy of auricular acupoint pressing combined with Zusanli acupoint injection of vitamin B1 for preventing chemotherapy-induced nausea and vomiting (CINV) in patients with breast cancer. A total of 120 patients receiving highly emetogenic chemotherapy were randomly assigned to four groups (n=30 each). Group A received a standard antiemetic regimen consisting of a 5-HT3 receptor antagonist and dexamethasone. Group B received additional auricular acupoint pressing, group C received Zusanli acupoint injection of vitamin B1, and group D received both interventions in addition to the standard regimen. Baseline characteristics were comparable among the four groups. The severity of nausea and vomiting was evaluated at multiple time points, while quality of life and physical status were assessed using the Karnofsky Performance Status (KPS) and Zubrod Performance Status scores. Significant differences in nausea severity were observed among the groups at all observation time points, and vomiting severity also differed significantly at most time points. The combined intervention group showed the most effective control of both symptoms. In addition, cumulative KPS and Zubrod scores differed significantly among the groups. Patients receiving the combined intervention demonstrated higher KPS scores and lower Zubrod scores, indicating improved functional status and treatment tolerance. Only mild adverse events were reported, and no treatment discontinuation occurred. Auricular acupoint pressing combined with Zusanli acupoint injection of vitamin B1, when added to standard antiemetic therapy, may synergistically improve the control of CINV and enhance quality of life and physical performance in patients with breast cancer.

Keywords: Breast Cancer; Chemotherapy; Nausea and Vomiting; Auricular Acupoint Pressing; Zusanli; Vitamin B1

1. Introduction

Breast cancer is the most common malignancy among women worldwide. Chemotherapy remains an essential component of its comprehensive treatment. However, chemotherapy frequently induces adverse reactions such as nausea and vomiting, which can compromise treatment tolerance and markedly impair patients' quality of life [1–2]. Effective prevention and management of chemotherapy induced nausea and vomiting, commonly referred to as CINV, are therefore critical for maintaining treatment adherence and improving overall outcomes. In current clinical practice, a combination of a 5 hydroxytryptamine type 3 receptor antagonist and dexamethasone is widely used as the standard antiemetic regimen. Although this strategy has improved symptom control in many patients, limitations remain. Drug related adverse effects and relatively high treatment costs may restrict its broader application in some clinical settings [3]. When NK 1 receptor antagonists cannot be routinely used, or when the standard regimen provides insufficient control, identifying safe, accessible, and effective adjunctive approaches becomes particularly important. In recent years, traditional Chinese medicine based supportive therapies have attracted increasing attention in the management of CINV. Auricular acupoint pressing has been widely applied because of its simplicity, non invasive nature, and favorable safety profile [4]. Acupoint injection, also known as water needle therapy, integrates the mechanical stimulation of acupuncture with the

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pharmacological effects of injected agents, offering an alternative therapeutic strategy for symptom control [5]. Vitamin B1, a key coenzyme involved in energy metabolism, plays an important role in maintaining normal neural function and promoting gastrointestinal motility [6]. Against this background, the present study was designed to evaluate the additional clinical benefit of combining auricular acupoint pressing with vitamin B1 injection at the Zusanli acupoint on the basis of a standard antiemetic regimen. By examining their potential synergistic effects, this study aims to provide clinical evidence supporting an integrated approach to the prevention and management of CINV.

2. Materials and Methods

2.1 Study Population

A total of 120 patients with breast cancer who were admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities between February 2024 and January 2025 were enrolled. Participants were randomly allocated into four groups using a computer generated random number table, with 30 patients in each group. To ensure the comparability of the groups, baseline characteristics including age, body mass index, clinical stage, and chemotherapy regimen were evaluated before intervention. The inclusion criteria were as follows: a pathological diagnosis of breast cancer [7]; first time receipt of highly emetogenic chemotherapy including anthracycline and or platinum based regimens; age greater than 18 years; a Karnofsky Performance Status score of 60 or higher [8]; and provision of written informed consent. The exclusion criteria included severe cardiac, hepatic, or renal dysfunction; ongoing hormone therapy; a previous history of gastrointestinal disease; current use of antiemetic medication; and the presence of psychiatric disorders or inability to cooperate with the study procedures. The study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities.

2.2 Grouping and Interventions

Group A, defined as the conventional antiemetic group, received a standard antiemetic regimen consisting of a 5 hydroxytryptamine type 3 receptor antagonist combined with dexamethasone. The dosage and administration were determined according to the Clinical Practice Guidelines for the Prevention and Treatment of Chemotherapy Induced Nausea and Vomiting [9].

Group B, referred to as the conventional plus auricular acupoint pressing group, received auricular acupoint pressing in addition to the standard antiemetic regimen used in group A. The selected auricular points included Shenmen, Endocrine, Spleen, Liver, Cardia, Stomach, and Sympathetic. After routine disinfection of the auricle with 75 percent alcohol, Vaccaria seeds were fixed onto the selected acupoints using adhesive patches. Each acupoint was pressed three to five times daily, approximately one minute per point, until the patient reported a sensation of soreness, distension, or warmth. The application began one day before chemotherapy. The patches were replaced every seventy two hours, with the two ears treated alternately.

Group C, referred to as the conventional plus Zusanli injection group, received vitamin B1 injection at the Zusanli acupoint in addition to the standard antiemetic regimen. The location of the Zusanli acupoint, also known as ST36, was determined according to the national standard of the People's Republic of China for nomenclature and location of meridian points, GB/T 12346 2021 [10]. The point is located on the anterolateral aspect of the lower leg, three cun below Dubi and one transverse finger breadth lateral to the anterior crest of the tibia. Vitamin B1 injection solution produced by Changzhou Pharmaceutical Factory Co., Ltd. with approval number H32021701 and a specification of 2 mL containing 100 mg was used. Each patient received 50 mg injected at the bilateral Zusanli acupoints, giving a total daily dose of 100 mg. After skin disinfection, the needle was inserted vertically to a depth of approximately 1.5 to 2.0 cm. When the sensation of needle arrival was achieved and aspiration confirmed the absence of blood, the solution was slowly injected.

Group D, defined as the combined intervention group, received both auricular acupoint pressing and vitamin B1 injection at the Zusanli acupoint in addition to the standard antiemetic regimen used in group A. Auricular acupoint pressing was initiated 24 hours before chemotherapy, while the vitamin B1 injection was administered one hour before chemotherapy on the treatment day.

2.3 Quality Control and Safety Management

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All procedures were performed by nursing staff who had received specialized training and were certified in traditional Chinese medicine related clinical techniques. A double checking system was implemented throughout the intervention process, and a three level reporting mechanism for adverse events was established to ensure patient safety and standardized management.

2.4 Outcome Measures

2.4.1 Severity of nausea and vomiting

The severity of nausea and vomiting was assessed using the gastrointestinal toxicity grading criteria from the Chinese version of the Common Terminology Criteria for Adverse Events, released by the United States Department of Health and Human Services on May 25, 2009 [11]. Nausea and vomiting were each classified into five grades.

For nausea, grade 0 indicated no nausea. Grade I referred to loss of appetite without changes in eating habits. Grade II indicated reduced oral intake without significant weight loss, dehydration, or malnutrition, with intravenous fluid supplementation lasting less than 24 hours. Grade III referred to insufficient caloric or fluid intake requiring intravenous hydration, tube feeding, or total parenteral nutrition for 24 hours or longer. Grade IV represented life threatening consequences. Grade V corresponded to death.

For vomiting, grade 0 indicated no vomiting within 24 hours. Grade I referred to one episode of vomiting within 24 hours. Grade II indicated two to five episodes within 24 hours requiring intravenous fluid supplementation for less than 24 hours. Grade III referred to six or more episodes within 24 hours requiring intravenous fluids or total parenteral nutrition for 24 hours or longer. Grade IV represented life threatening consequences, and grade V indicated death.

To comprehensively evaluate the symptom burden throughout the chemotherapy process, daily symptom grades were recorded and analyzed from day 1 to day 7 after the initiation of the first and second chemotherapy cycles.

2.4.2 Quality of life assessment using the Karnofsky performance status score

Patients' quality of life was evaluated using the Karnofsky Performance Status scale [8]. Scores range from 0 to 100, with higher scores indicating better overall health status and a greater capacity to tolerate treatment related adverse effects.

2.4.3 Physical performance assessment using the Zubrod Performance Status score

Physical performance was evaluated using the Zubrod Performance Status scale, also known as the ECOG or WHO performance status scale [12]. The scale contains five levels ranging from 0 to 4. Higher scores reflect poorer functional capacity, and scores of three or above indicate markedly impaired physical performance.

2.4.4 Data collection and calculation of cumulative cycle scores

All baseline data were collected within 24 hours before the initiation of the first chemotherapy cycle. To capture the sustained effect of the interventions on functional status across chemotherapy cycles, cumulative cycle scores for KPS and ZPS were calculated. Specifically, the cumulative value for each patient was defined as the sum of the scores obtained on day 7 after completion of the first and second chemotherapy cycles. This cumulative indicator incorporates information from two time points and therefore provides a more comprehensive assessment of treatment related changes in functional status than a single time point comparison.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Continuous variables following a normal distribution were expressed as mean ± standard deviation and analyzed using one way analysis of variance. Variables not conforming to a normal distribution were expressed as median with interquartile range and analyzed using the Kruskal Wallis H test. Categorical or ordinal variables were presented as counts and analyzed using the chi square test or Fisher exact test, while ordinal data were also evaluated using the Kruskal Wallis H test. Pairwise comparisons were conducted with Bonferroni correction. A two sided P value less than 0.05 was considered statistically significant.

3. Results

3.1 Comparison of Baseline Characteristics

Table 1 summarizes the baseline characteristics of patients in the four groups. No statistically significant differences were observed among the groups with respect to age, body mass index, clinical stage, or chemotherapy regimen, with all P values greater than 0.05. These findings indicate that the baseline characteristics were well balanced across groups and that the groups

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were comparable before intervention.

3.2 Pre Chemotherapy Biochemical Indicators

Before chemotherapy, liver function indices including alanine aminotransferase and aspartate aminotransferase, renal function indicators including blood urea nitrogen and creatinine, as well as electrolyte levels including serum potassium, sodium, and calcium were compared among the four groups. No statistically significant differences were observed in any of these parameters, with all P values greater than 0.05.

Table 1. Comparison of Baseline Clinical Characteristics among the Four Groups

Group / Statistic	Age (years)	BMI (kg/m²)	Clinical stage (I–II / III–IV)	Chemotherapy type (Postoperative / Neoadjuvant or salvage)
Group A	48.00(43.00,52.00)	22.35(21.47,25.90)	19/11	10/20
Group B	49.00(40.75,55.25)	22.85(21.25,25.14)	16/14	14/16
Group C	52.00(47.75,55.00)	22.62(21.50,25.80)	18/12	13/17
Group D	45.00(41.00,53.50)	23.05(21.39,25.41)	23/7	14/16
Z/x²	5.894	0.153	3.732	1.466
P-value	0.117	0.985	0.277	0.685

3.3 Safety Analysis and Adverse Events

Safety was evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0, released by the National Cancer Institute [13]. The analysis focused on both laboratory abnormalities and non laboratory adverse events observed during the study period. First, dynamic monitoring after completion of the first and second chemotherapy cycles revealed that the most frequently observed laboratory abnormalities were grade 1 to 2 elevations in liver enzymes and hypokalemia. No grade 3 or higher laboratory abnormalities were detected. Moreover, the incidence of these laboratory abnormalities showed no statistically significant differences either between the groups or across the two chemotherapy cycles, with all P values greater than 0.05. Second, all non laboratory adverse events were related to the study interventions. Three patients experienced grade 1 skin pruritus associated with auricular acupoint pressing, accounting for 5.0 percent of participants. Two patients reported grade 2 localized pain at the injection site following acupoint injection, representing 3.33 percent of cases (Table 2). All symptoms were mild and resolved after symptomatic management. Importantly, none of these adverse events resulted in interruption or discontinuation of chemotherapy.

Table 2. Incidence of Laboratory Abnormalities after Two Chemotherapy Cycles [n (%)]

After the first chemotherapy cycle (C1)	Group A (n=30)	Group B (n=30)	Group C (n=30)	Group D (n=30)	P-value
After the first chemotherapy cycle (C1)					
ALT elevation (≥3× ULN, grade 3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
ALT or AST elevation (grade 1–2)	2 (6.7)	1 (3.3)	3 (10.0)	1 (3.3)	0.650
Hypokalemia (grade 1–2)	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)	0.550
After the second chemotherapy cycle (C2)					
ALT elevation (≥3× ULN, grade 3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
ALT or AST elevation (grade 1–2)	3 (10.0)	2 (6.7)	2 (6.7)	1 (3.3)	0.750
Hypokalemia (grade 1–2)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	0.550
Highest abnormality grade during any cycle					
Any grade ≥3 laboratory abnormality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000

3.4 Comparison of Nausea Severity

The distribution of nausea grades among the four groups was compared at the beginning and end of the two chemotherapy cycles, including C1D1, C1D7, C2D1, and C2D7. Statistically significant differences were observed in nausea severity among the groups at all four time points, with all P values less than 0.001. Detailed results are presented in Table 3.

3.5 Comparison of Vomiting Severity

Analysis of vomiting grades revealed that the distribution differed significantly among the four groups at several time points during the chemotherapy cycles, particularly from day 2 to day 6 of the first cycle. These differences reached statistical significance with P values below 0.05. In contrast, no statistically significant differences were observed on the first

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or the last day of each chemotherapy cycle. Specifically, the comparisons yielded P values of 0.109 for C1D1, 0.392 for C1D7, 0.099 for C2D1, and 0.392 for C2D7. The detailed distribution of vomiting grades across groups and time points is presented in Table 4.

Table 3. Comparison of Nausea Severity at the Beginning and End of Chemotherapy Cycles among the Four Groups [n (%)]

Group	Grade	First cycle (C1)		Second cycle (C2)		Test statistic
		Start (D1)	End (D7)	Start (D1)	End (D7)	F, P-value
Group A	Grade 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Grade I	30 (100.0)	30 (100.0)	29 (96.7)	30 (100.0)	
	Grade II	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Group B	Grade 0	21 (70.0)	21 (70.0)	22 (73.3)	20 (66.7)	
	Grade I	9 (30.0)	9 (30.0)	8 (26.7)	10 (33.3)	
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D1: 66.938
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D7: 66.938
Group C	Grade 0	21 (70.0)	21 (70.0)	21 (70.0)	21 (70.0)	C2D1: 68.848
	Grade I	9 (30.0)	9 (30.0)	9 (30.0)	9 (30.0)	C2D7: 65.777
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Group D	Grade 0	30 (100.0)	30 (100.0)	30 (100.0)	30 (100.0)	C1D1: 0.000
	Grade I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D7: 0.000
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C2D1: 0.000
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C2D7: 0.000

Note: C1 indicates the first chemotherapy cycle and C2 indicates the second chemotherapy cycle. D represents the specific day within the cycle. For example, C1D1 refers to day 1 of the first chemotherapy cycle.

Table 4. Comparison of Vomiting Severity at the Beginning and End of Chemotherapy Cycles among the Four Groups [n (%)]

Group	Grade	First cycle (C1)		Second cycle (C2)		Test statistic
		Start (D1)	End (D7)	Start (D1)	End (D7)	P-value
Group A	Grade 0	28 (93.3)	29 (96.7)	26 (86.7)	29 (96.7)	
	Grade I	2 (6.7)	1 (3.3)	4 (13.3)	1 (3.3)	
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Group B	Grade 0	30 (100.0)	30 (100.0)	29 (96.7)	30 (100.0)	
	Grade I	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D1: 6.051
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D7: 3.000
Group C	Grade 0	30 (100.0)	30 (100.0)	29 (96.7)	30 (100.0)	C2D1: 6.263
	Grade I	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	C2D7: 3.000
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Group D	Grade 0	30 (100.0)	30 (100.0)	30 (100.0)	30 (100.0)	C1D1: 0.109
	Grade I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C1D7: 0.392
	Grade II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C2D1: 0.099
	Grade III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	C2D7: 0.392

Note: C1 indicates the first chemotherapy cycle and C2 indicates the second chemotherapy cycle. D represents the specific day within the cycle. For example, C1D1 refers to day 1 of the first chemotherapy cycle.

3.6 Between Group Comparison of Cumulative KPS and ZPS Scores

The Kruskal Wallis H test showed significant differences in the cumulative KPS and ZPS scores among the four groups. For KPS, the test yielded $H = 78.590$ with $P < 0.001$. For ZPS, the result was $H = 44.875$ with $P < 0.001$. These findings indicate that the interventions produced measurable differences in functional outcomes across the study groups. Further pairwise comparisons demonstrated that the cumulative KPS score in group D was significantly higher than those observed in groups A, B, and C. At

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the same time, the cumulative ZPS score in group D was significantly lower than in the other three groups, with all comparisons reaching statistical significance. Taken together, these results suggest that the combined intervention provided the greatest benefit in improving both quality of life and overall physical performance during chemotherapy.

4. Discussion

Chemotherapy induced nausea and vomiting remains one of the most frequent and distressing adverse events experienced by patients with breast cancer during systemic treatment. These symptoms can substantially impair nutritional intake, reduce treatment adherence, and ultimately diminish quality of life [9]. Although antiemetic regimens based on 5 hydroxytryptamine type 3 receptor antagonists are widely applied in clinical practice, a proportion of patients still experience insufficient symptom control. In addition, adverse effects such as constipation and headache may limit patient tolerance to these medications [14]. Against this clinical background, identifying safe and effective adjunctive approaches has become an important focus in supportive cancer care. The present study explored a combined strategy integrating auricular acupoint pressing and vitamin B1 injection at the Zusanli acupoint on the basis of a conventional antiemetic regimen, aiming to provide a practical integrative option for the prevention and management of CINV. The findings of this study suggest that the addition of these two traditional medicine based interventions to the standard antiemetic regimen resulted in meaningful clinical benefits. Compared with the conventional regimen alone or with the addition of only one traditional technique, the combined intervention achieved more effective control of nausea and vomiting and was associated with better overall patient status.

From the perspective of symptom control, the combined intervention group demonstrated a clear advantage in reducing both nausea and vomiting under the same background antiemetic regimen. The potential mechanisms may involve complementary regulatory pathways. Auricular acupoint pressing stimulates several functional points such as Shenmen and Sympathetic, which are believed to calm the mind and regulate autonomic nervous system activity. At the same time, stimulation of points associated with the stomach and cardia may help harmonize gastric function and suppress the upward disturbance that contributes to nausea and vomiting [15–16]. In parallel, Zusanli, a key point of the stomach meridian of foot Yangming, has long been regarded as an important point for strengthening digestive function and supporting overall vitality. Injection of vitamin B1 at this location provides both mechanical stimulation and pharmacological activity. Vitamin B1 participates in energy metabolism, supports neural function, and may contribute to the regulation of gastrointestinal motility [17]. Through these complementary mechanisms, the two interventions may form a multi level regulatory network that targets different aspects of the CINV pathway, thereby enhancing symptom control.

Beyond symptom relief, the combined intervention also demonstrated broader functional benefits. Patients in group D achieved the highest cumulative KPS scores and the lowest ZPS scores, indicating better preservation of physical capacity and daily functional ability during chemotherapy. This observation suggests that the benefit of the combined strategy extends beyond simple antiemetic control. One plausible explanation is that improved management of nausea and vomiting reduces energy loss and nutritional insufficiency during treatment. At the same time, the tonic effect traditionally attributed to the Zusanli acupoint, together with the metabolic regulatory role of vitamin B1, may help support systemic resilience and enhance tolerance to chemotherapy [18].

An additional observation from this study is that clinically meaningful benefits were achieved even without the use of NK 1 receptor antagonists. In settings where the guideline recommended triple antiemetic regimen cannot be routinely implemented, the combined intervention evaluated in this study may therefore represent a practical adjunctive strategy to improve symptom control.

When compared with previous research, the present findings are broadly consistent with earlier reports examining individual traditional medicine interventions for CINV. For example, Xu Xuefen and colleagues reported that auricular acupoint pressing could effectively prevent and alleviate chemotherapy related nausea and vomiting [19]. Similarly, Wang Wei and colleagues observed that vitamin B1

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injection at the Zusanli acupoint improved both acute and delayed phases of CINV in patients receiving chemotherapy [20]. Building upon these earlier observations, the present study employed a four group randomized controlled design. This approach not only confirmed the effectiveness of each individual technique but also provided evidence supporting their synergistic effect when used together, thereby offering stronger clinical evidence for optimizing integrative antiemetic strategies.

Several limitations should be acknowledged. First, the background antiemetic regimen consisted of a dual therapy rather than the guideline recommended triple regimen that includes an NK 1 receptor antagonist for highly emetogenic chemotherapy. While this design allowed the study to focus on the additional benefit of traditional medicine interventions, the results cannot be directly compared with outcomes achieved under the current highest standard antiemetic protocols. Consequently, the findings are most applicable to clinical settings where dual therapy remains in use and additional symptom control is needed. Caution is warranted when extrapolating these results to centers that routinely implement triple antiemetic regimens. Second, this study was conducted at a single center with a relatively limited sample size. Because of the nature of the interventions, blinding was not feasible, which may introduce potential performance or measurement bias. Future investigations involving multicenter designs and larger sample sizes, ideally using the triple antiemetic regimen as the background standard, would help further clarify the incremental clinical value and cost effectiveness of this combined approach.

In summary, the integration of auricular acupoint pressing with vitamin B1 injection at the Zusanli acupoint represents a simple and safe adjunctive therapy that can work synergistically with conventional antiemetic treatment. This combined strategy significantly improves the control of chemotherapy induced nausea and vomiting in patients with breast cancer while also contributing to better physical performance and quality of life. Such an approach may provide a valuable complementary option for CINV management, particularly in clinical settings where optimization of supportive care is needed under specific resource conditions.

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Ethical approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities. Written informed consent was obtained from all participants before enrollment.

Author contributions

Dalang Fang supervised the study. All authors were involved in study design, data collection, data analysis, and manuscript preparation. All authors reviewed and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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