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Original Article

The effects of acupuncture at different intervention time points on nausea and vomiting caused by cisplatin chemotherapy in patients with lung cancer

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Abstract: Objective: To explore the effects of the timing of acupuncture intervention on nausea and vomiting (CINV) caused by cisplatin in patients with lung cancer. Methods: A total of 105 patients with lung cancer were randomly divided into a pre-chemotherapy acupuncture group (PRG) who receive acupuncture 30 minutes before chemotherapy, a post-chemotherapy acupuncture group (POG) who receive acupuncture 30 minutes after chemotherapy, and a control group who were not given acupuncture intervention. Complete remission (CR) rate and the response rate of chemotherapy-related nausea and vomiting after acupuncture intervention at different times, frequency of nausea and vomiting and their total score on INVR scale were compared. Results: There were statistically significant differences in the response and CR rates between the PRG, POG and control group 3 days before chemotherapy (all $P < 0.05$). In terms of INVR scores, no statistical difference between the POG and control group on the first day of chemotherapy, but the PRG differed significantly from the POG and control group ($P < 0.05$). On the 2nd to 7th day of chemotherapy, the difference between the three groups was statistically significant ($P < 0.05$). Conclusion: Acupuncture before chemotherapy can effectively reduce the frequency of nausea and vomiting associated with cisplatin chemotherapy in lung cancer patients, improve the effectiveness of CINV treatment, and can be widely promoted in clinic.

Keywords: Timing of intervention, nausea, vomiting, acupuncture, chemotherapy

Introduction

The incidence of cancer has increased annually, and chemotherapy has a pivotal position in cancer treatment [1]. Chemotherapy induced nausea and vomiting (CINV) cannot be ignored. Cisplatin is a high emetic risk intravenous chemotherapy in which emesis occurs in 100% cisplatin-treated patients [2, 3]. Cisplatin-based treatment accounts for 70-80% of the chemotherapy regimens in China [4]. Although aprepitant and torsitron can prevent vomiting effectively, they are sold at high prices and accompanied by gastrointestinal reactions such as constipation and bloating, which the patients do not tolerate well [5]. A number of studies have shown that acupuncture has an advantage in treating CINV [6-10]. By summarizing the studies on early acupuncture treatment of CINV, we find that effective acupuncture interventions for CINV are centered on Zusanli and Neiguan. However, there are obvious differences in the timing of acupuncture intervention in these studies. Whether the timing of acupuncture intervention has an effect on the efficacy of acupuncture treatment of CINV needs to be clarified. In this study, acupuncture intervention was given before and after chemotherapy, and the effect of the different timing of treatment on CINV was observed in a random controled study.

Materials and methods

Patient sourcing

The patients were diagnosed with lung cancer and experienced nausea and vomiting during chemotherapy. A total of 105 patients were enrolled from December 2014 to December

2017 in Beijing Traditional Chinese Medicine Hospital affiliated with Capital Medical University.

Clinical trial protocols of this study were reviewed and signed by the Ethics Committee of Beijing Traditional Chinese Medicine Hospital affiliated with Capital Medical University (2015BL-052-02). The clinical trial program was registered (registration number: ChiCTR-INR-16010175).

Inclusion criteria were: patients with lung cancer confirmed by pathological diagnosis; 18-75 years old; patients who received 3 or more cycles of cisplatin-based dual-drug chemotherapy regimen; Karnofsky score > 60 points (The total score is 0-100 points, the higher the score, the better the patient's health; if it is less than 60 points, chemotherapy may not be applicable); patients who sign an informed consent.

Exclusion criteria were: patients with serious diseases in heart, liver, kidney, immune and hematopoietic system; pregnant women and lactating women; patients with brain metastases, increased intracranial pressure, gastrointestinal obstruction, severe liver and kidney dysfunction; patients with refractory vomiting caused by brain tumors, and cerebrovascular diseases; patients with abnormal blood coagulation, thrombocytopenia or bleeding disorders; patients with depression, anxiety, mental illness and cognition disorders; patients who cannot receive acupuncture treatment due to fear of needles and allergies to stainless steel needles.

Withdrawal criteria were: patients with serious complications and life-threatening events during acupuncture treatment; patients who received treatment that was not allowed in this study; patients who wanted to withdrawal.

Sample size calculation

According to the previous results, the CR rate of tropisetron for the prevention of nausea and vomiting caused by chemotherapy was 32% and 59%, respectively. It was expected that treatment group would have a 25% higher CR rate than control group ($\alpha = 0.05$, $\beta = 0.2$, 80% CI). According to the following formula

$$n = \frac{\pi_0(1 - \pi_0)(\mu_\alpha + \mu_\beta)^2}{\delta^2}$$

The sample size is 35 cases in each group with 15% shedding rate.

Case inclusion and data diversity

A total of 134 patients were recruited during the study period. 105 patients who met the inclusion and exclusion criteria and signed the informed consent were included, including 35 patients in the PRG, 35 patients in POG, and 35 patients in the control group. During the study period, there were 9 cases that withdrew (with a shedding rate of 8.57%), of which 4 cases withdrew their informed consent, 4 cases were lost to follow-up, and 1 case was excluded because he did not meet the inclusion criteria.

Full analysis set (FAS): 100 cases, 32 cases in PRG, 34 cases in POG, and 34 cases in the control group. In 9 cases of withdraw, 4 patients completed 2 follow-ups and were analyzed with FAS. Per Protocol Analysis Set (PPS); 96 cases, 30 cases in PRG, 32 cases in POG, and 34 cases in the control group. Safety data set (SS): 101 cases, 34 cases in PRG, 33 cases in POG, and 34 cases in the control group.

Grouping plan

A random number table was used for grouping with SPSS 22.0. There were 105 opaque and sealed envelopes were coded according to the order of the included patients. The envelopes were arranged in order of patient enrollment. Then, 105 random numbers were assigned to every envelope. Numbers 1-35 were included in PRG, 36-71 were included in POG and 72-105 were enrolled in control group.

Treatment methods

The control group (non-acupuncture group) was given 5 mg intravenous infusion of tropisetron hydrochloride 15 minutes before chemotherapy and drugs (such as promethazine, tramadol, promethazine, tramadol, etc.) that might affect the symptoms of nausea and vomiting were not given.

The acupuncture groups are divided into two groups: one group underwent acupuncture 30 minutes before chemotherapy, and one group received acupuncture 30 minutes after chemotherapy, that is, 30 minutes after intravenous infusion of cisplatin.

The acupuncture treatment centered on Neiguan (bilateral) and Zusanli (bilateral) acupoints; a reinforcing-reducing method was performed on Neiguan acupoints and the twirling and rotating method was applied on Zusanli acupoints and the needles were kept in for 30 minutes.

Treatment course was once a day for 5 consecutive days. The needles used in the study were 0.25 × 40 mm disposable acupuncture needles (Guizhou Andi Medical Devices Co., Ltd.). In order to avoid any differences in acupuncture techniques caused by administration, physicians with 3 years of experience performed the acupuncture for patients. The acupuncture site and the hands of the acupuncturist were disinfected with 75% alcohol. Deqi was defined as feelings of neuropathic pain, numbness, and swelling at the acupuncture points after needle insertion.

Efficacy evaluation

Blind evaluation techniques were used for efficacy evaluation and statistical analysis, which are independent of researchers, evaluators and data analysts.

Outcome measures

Severity of nausea and vomiting: Vomiting is defined as the forceful expulsion of gastric and intestinal contents through the mouth, excluding retching. The severity of nausea and vomiting was accessed by National Cancer Institute Common Toxicity Criteria 4.0 (NCI-CTC 4.0). The number of cases of nausea and vomiting was used to calculate the CR rate and effectiveness.

Index of nausea, vomiting and retching (INVR) scale: A scale scoring 8-40 points measures the number, severity and duration of nausea, vomiting and retching through 8 items and 5 quantitative standards. The higher the score, the more severe the CINV.

Simple nutrition assessment questionnaire (SNAQ) was used to evaluate the nutritional status of patients. The questionnaire includes 6 items covering the appetite, diet, and taste of the patient. Each item scored 1-5 points.

Adverse reactions

Adverse reactions (symptoms and signs) of patients during the treatment were recorded, including onset time, duration, severity, treatment measures, needle breaks, bleeding at the acupuncture site, etc.

Follow up

The researchers recorded data from 16:00 to 17:00 daily from the beginning to the end of chemotherapy. The intervention treatment in this study lasted for 5 days and was followed up for 16 days for a total of 21 days. If the patient is not followed up after chemotherapy, it iwa regarded as a case of lost to follow up and was not recorded.

Statistical methods

Excel was used to establish the database, and SPSS 20.0 software was used for the statistical analysis. All hypothesis tests used a two-sided test. The two-sample t test was used for the measurement data, the chi-square test was used for the classification and grade data, and the Fisher data accurate test is used for the data with the theoretical frequency less than 5. Nausea frequency: The three groups were analyzed by single factor ANOVA and compared by LSD analysis. $P < 0.05$ means the difference was statistically significant.

Results

There was no significant statistical difference between the baseline data of the two groups Baseline characteristics include age, education level, occupational status, medical history, history of cancer treatment, and KPS score, etc. FAS analysis was used for baseline data (**Table 1**). The results showed that there was no significant statistical difference between the baseline data of the two groups ($P > 0.05$), and the baseline data was comparable.

Table 1. Baseline data (FAS)

	PRG (n=32)	POG (n=34)	Control (n=34)	P
Age				0.560
Mean (standard deviation)	59.64 (6)	58.73 (9)	60.12 (8)	
Range	46-69	37-69	38-69	
Education level				0.945
Middle school	14	18	17	
High school and college	15	14	14	
Undergraduate	3	2	3	
Staging				0.943
I	4	5	4	
II	6	7	5	
III	6	7	6	
IV	16	15	19	
Cisplatin dose (standard deviation)	68.75	69.2	67.81	0.217
Kps score (mean)	70	80	70	0.412

The difference was statistically significant between PRG, POG and the control group in the first 3 days of chemotherapy

The CR rate of nausea and vomiting was expressed as cases of complete remission of nausea and vomiting, and the effective rate was a ratio of no nausea + mild nausea, unimpaired appetite, and cases of CR and partial remission (PR) of vomiting. The difference was statistically significant between PRG, POG and the control group in the first 3 days of chemotherapy ($P < 0.05$, **Tables 2** and **3**).

Acupuncture can effectively reduce the frequency of nausea and frequency of acute vomiting (d1-4 days) was significantly lower in PRG and POG

The frequency of nausea from day 1 to day 4 after chemotherapy was better in the PRG, POG than in the control group, suggesting that acupuncture can effectively reduce the frequency of nausea ($P < 0.05$). The frequency of acute vomiting (d1-4 days) was significantly lower in PRG and POG (**Table 4**).

There was a statistical difference between PRG and controls, POG and PRG

In terms of the total INVR scores, there was no statistical difference between POG and controls, but there was a statistical difference between PRG and controls, POG and PRG ($P < 0.05$, **Table 5**).

SNAQ has a statistical difference between the three groups

There was no significant difference in nutritional status on the first day (V1), which were comparable ($P = 0.673$). The SNAQ scores decreased at day 3 and then gradually increased. PRG showed the largest increase. On the 7th day, there was a significant difference between the three groups ($P = 0.44$) (**Figure 1** and **Table 6**).

Discussion

Chemotherapy is the most common treatment option for patients with lung cancer. Nausea and vomiting are key factors affecting the success of chemotherapy. According to the National Comprehensive Cancer Network (NCCN) antiemetic guidelines [11], 5-HT3 receptor antagonists are currently used for chemotherapy-related nausea and vomiting, however, it has side effects such as constipation, diarrhea, and even nausea and vomiting. Studies have shown that although there are a variety of potent antiemetic drugs available to choose from, 20% of patients still need to delay chemotherapy due to severe nausea and vomiting, and 35% of patients refuse chemotherapy because of severe vomiting reactions [12-15].

Studies have shown that acupuncture therapy can effectively relieve CINV, but the timing of the acupuncture in these studies varies, and the relationship between the timing of acupuncture and treatment efficacy is not clear

Table 2. Evaluation of nausea symptoms in NCI-CTC 4.0 (PPS)

Response rate	Timing	PRG	POG	Control	P
CR	Day 1	6 (17%)	9 (25%)	7 (20%)	0.043
	Day 2	2 (6%)	1 (3%)	1 (3%)	0.045
	Day 3	4 (11%)	1 (3%)	1 (3%)	0.034
PR	Day 1	24 (69%)	22 (63%)	22 (63%)	0.298
	Day 2	22 (63%)	21 (60%)	19 (54%)	0.612
	Day 3	25 (63%)	24 (57%)	20 (49%)	0.306
Invalid	Day 1	5 (14%)	4 (12%)	6 (17%)	0.119
	Day 2	13 (31%)	13 (37%)	15 (33%)	0.117
	Day 3	6 (26%)	10 (40%)	14 (40%)	0.023

Table 3. Evaluation of vomiting by NCI-CTC 4.0 (PPS)

Response rate	Timing	PRG	POG	Control	P
CR	Day 1	31 (88.6%)	29 (82.9%)	17 (49%)	0.044
	Day 2	24 (68.6%)	20 (57.1%)	15 (43%)	0.057
	Day 3	23 (65.7%)	20 (57.1%)	14 (40%)	0.041
PR	Day 1	3 (8.6%)	2 (5.7%)	5 (14.3%)	0.345
	Day 2	7 (20%)	8 (22.9%)	10 (28.6%)	0.641
	Day 3	9 (25.7%)	7 (20%)	12 (34.3%)	0.578
Invalid	Day 1	1 (2.9%)	0 (0%)	13 (37%)	0.034
	Day 2	4 (11.4%)	7 (20%)	10 (29%)	0.047
	Day 3	3 (8.6%)	8 (22.9%)	9 (25.7%)	0.230

[16-18]. This study primarily focused on the timing of acupuncture intervention. Patients with lung cancer who were treated with cisplatin were enrolled. All patients received antiemetic therapy with ondansetron. Acupuncture therapy is performed based on meridian theory, which stimulates the meridian points to restore natural healing abilities. The selected acupoints, Zusanli and Neiguan, have the effects of strengthening the spleen and stomach, regulating Qi and vomiting. Bilateral zusanli points are two of the eight points for eliminating heat from the stomach. Neiguan connects the Pericardium channel with the San Jiao, and is commonly used to help relieve nausea, upset stomach, motion sickness, carpal tunnel syndrome, and headaches in clinical research.

This study found that acupuncture performed 30 minutes before chemotherapy can effectively reduce the frequency of CINV. Its efficiency and complete remission rate exceeded that of acupuncture treatment performed 30 minutes after chemotherapy. At the same time, in 7 days following chemotherapy, INVR scores showed a trend of first increasing and then decreasing, but acupuncture before chemotherapy still had certain advantages. INVR can be broadly categorized as acute (occurring within 24 hours of therapy), delayed (persisting for 6-7 days after therapy), or anticipatory (occurring prior to chemotherapy administration). It can be seen that acupuncture combined with tropisetron can relieve acute and delayed vomiting. Several studies have shown that combined treatment is better than antiemetics alone [19-21]. Fu Qiang, et al. [22] had observed the effect of ondansetron combined with acupuncture of bilateral Neiguan and Zusanli on CINV. After 24 and 96 hours of treatment, the control rates of nausea and vomiting in the treatment group were better than those in the control group, with fewer toxic and side effects.

Rithirangsriroj et al. [23] explored the effect of acupuncture at Neiguan acupoint on patients with gynecological malignant tumors. The enrolled patients were all in the first cycle of chemotherapy. Neiguan acupoint was stimulated in acupuncture group before chemotherapy, and the administration group was given 8 mg of ondansetron intravenously half an hour before chemotherapy. The results showed that the complete remission rate of CINV (52.8% VS 35.7%, P = 0.02) and the complete remission rate of delayed CINV (65.7% VS 45.7%, P = 0.004) as well as the quality of life scores were significantly higher in the acupuncture group than in the administration group; while the incidence of delayed nausea, severity of nausea, and antiemetic doses were lower than in the administration group. In terms of delayed nausea and vomiting, Zhou Li [24] found that granisetron combined with acupuncture for CINV has a significant advantage over the control group on 3rd day to 5th day of chemotherapy. Sima Lei [10] found patients with vomiting caused by cisplatin chemotherapy and ineffective to ondansetron exhibited 45.16% effective rate by acupuncture treatment, which is better than the

Table 4. Evaluation of nausea frequency on INVR scale

Group	Cases	D1	D2	D3	D4	D5	D6	D7
PRG	30	1.11±0.47	3.09±1.36	3.74±1.29	3.80±1.49	3.34±1.45	2.31±1.21	1.34±0.73
POG	32	1.03±0.17	2.97±1.56	4.09±1.29	4.49±1.46	3.60±1.37	2.89±1.51	1.91±1.17
Control group	34	1.06±0.34	2.69±1.57	4.06±1.55	4.34±1.53	3.63±1.37	2.83±1.34	1.86±1.29
F		3.317	3.339	3.321	3.382	2.924	0.548	3.308
P		0.048	0.051	0.049	0.041	0.52	1.000	0.037
PRG vs POG		0.047	0.050	0.047	0.032	0.52	0.099	0.025
PRG vs Control		0.049	0.050	0.047	0.032	0.53	0.099	0.041
POG vs Control		0.047	0.050	0.047	0.032	0.57	0.099	0.050

Table 5. Evaluation of total scores of three groups of INVR

Grouping	Cases	D1	D2	D3	D4	D6	D7
PRG	30	5.11±0.53	10.54±5.85	13.89±4.51	14.57±5.74	3.94±0.67	2.29±0.39
POG	32	5.15±0.98	10.34±5.31	14.51±5.91	15.23±5.82	4.67±0.78	3.80±0.64
Control group	34	5.34±1.77	10.86±4.64	15.90±4.59	17.17±5.32	5.44±0.92	4.50±0.30
PRG vs POG		0.040	0.036	0.027	0.048	0.043	0.036
PRG vs Control		0.015	0.005	0.008	0.001	0.026	0.045
POG vs Control		0.495	0.015	0.029	0.035	0.015	0.032

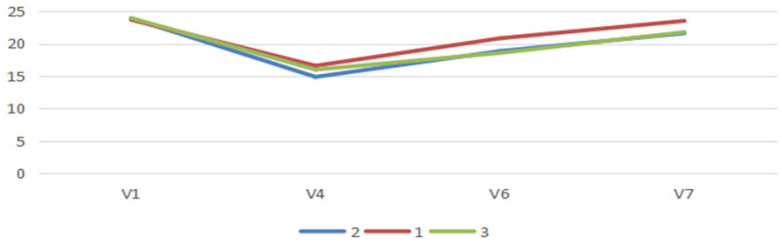

Figure 1. Comparison of nutritional status.

Table 6. Nutritional status

Timing	PRG	POG	Control group	P
Day 1	23.7	23.9	23.9	0.673
Day 3	16.6	14.9	16	0.098
Day 5	20.8	18.9	18.5	0.055
Day 7	23.5	21.6	21.8	0.044

control group and improves the quality of life of the patients.

This study revealed that acupuncture at Neiguan and Zusanli before chemotherapy can effectively relieve CINV. The research may have limitations due to research methods or the number of researchers selected.

This study found that acupuncture before chemotherapy can better relieve CINV and reduce the frequency of vomiting and nausea. Acupuncture combined with tropisetron can improve the efficiency and remission rate of CINV with low cost and the simple operation, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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