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Therapeutic effect of low frequency electric pulse therapy on cisplatin-based chemotherapy-induced nausea and vomiting in patients with lung adenocarcinoma

A prospective controlled study

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Abstract

To explore the efficacy of low-frequency electric pulse therapy (LFEPT) combined with 2 antiemetics in the prevention and treatment of cisplatin-based chemotherapy-induced nausea and vomiting (CINV) in patients with lung adenocarcinoma. A total of 82 patients with lung adenocarcinoma who received cisplatin-based chemotherapy were randomly divided into the experimental group (n=41) and control group (n=41) by random numerical table method. The experimental group was treated with LFEPT combined with 2 antiemetic drugs (tropisetron hydrochloride and dexamethasone hydrochloride), while the control group was treated with the same 2 antiemetic drugs. Revised index of nausea and vomiting and retching (R-INVR) and Functional Living Index-Emesis (FLIE) scale were used to quantitatively evaluate the symptoms of nausea and vomiting after chemotherapy, and the effect of LFEPT in the prevention and treatment of CINV was observed. The baseline characteristics had no statistical difference between the 2 groups. The degree of nausea reaction, vomiting, and dry retching were similar in 2 groups on the first day after chemotherapy. However, the degree of nausea reaction, vomiting, and dry retching were significantly improved in the experimental group than that of the control group on 2 to 5 days with all $P<.05$. The score of FLIE had no difference between the 2 groups on the first day after chemotherapy (84.05 vs 82.69, $P=.30$), and the score was significantly higher in experiment group on day 6 compared with the control group (103.71 vs 89.38, $P=.02$). The side effects had no difference between the 2 groups. The LFEPT can significantly ameliorate CINV in patients with lung adenocarcinoma, which is worthy of clinical application.

Abbreviations: 5-HT3 = 5-hydroxytryptamine; CINV = chemotherapy-induced nausea and vomiting; FLIE = functional living index-emesis; KPS = Karnofsky performance status; LFEPT = low-frequency electric pulse therapy; R-INVR = revised index of nausea and vomiting and retching; SD = standard deviation; TCM = Traditional Chinese Medicine.

Keywords: antiemetic, chemotherapy, cisplatin, low-frequency electric pulse therapy device, nausea and vomiting

1. Introduction

Cancer, as one of the main causes of death worldwide, is a serious threat to human life and health.[1] As one of the main cancer treatments, chemotherapy plays an important role in preoperative neoadjuvant therapy, translational therapy, postoperative adjuvant therapy, and tumor maintenance therapy.[2] However, as a systemic, nonspecific treatment, chemotherapy will have adverse effects on the normal cells and organs of the body, resulting in a variety of adverse reactions.[3] Among these adverse reactions, chemotherapy-induced nausea and vomiting (CINV) is the most common one. The dehydration, electrolyte disorder, malnutrition, fear, pessimism, and negative emotions caused by CINV may greatly affect treatment compliance. Suffering from this, patients may unable to complete the full duration of the chemotherapy course, which dramatically affects the therapeutic effect.[4–6] Among all chemotherapeutic drugs, cisplatin has the highest incidence of vomiting, about 90%–100%.[7] As a first-generation platinum drug, cisplatin has wide indications and a low price and is widely used in clinics.[7] Therefore, how to reduce the incidence of CINV caused by cisplatin-based chemotherapy is a clinical problem to be solved urgently.

Nowadays, many drugs have been used for the prevention and treatment of CINV, including 5-HT_3 receptor antagonists, dexamethasone, NK-1 receptor antagonist, palonosetron, and olazantan.[4–6] To a certain extent, these drugs can prevent the occurrence of acute and delayed CINV, but some drugs are

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expensive, increasing the economic burden of low-income chemotherapy patients, and also have certain side effects.[4–6] Recently, multiple studies have shown that Traditional Chinese Medicine (TCM) therapy, such as acupuncture, acupoint injection, acupoint application, acupoint massage, and moxibustion, has a definite effect on the prevention and treatment of CINV, which have a great effect on alleviating gastrointestinal side effects after chemotherapy.[8–10] The low-frequency electric pulse therapy (LFEPT) instrument, an in vitro transdermal nerve electrical stimulation therapy instrument, can stimulate the body acupoints by sending out the low-frequency pulse of a specific frequency. In addition. the low-frequency pulse therapy instrument can be carried out in the ward with the characteristics of a simple operation and no pain for patients. The effect of the instrument on the prevention and treatment of CINV in patients with advanced gastric cancer has been identified in the previous study.[11] However, no studies have reported its therapeutic effects on patients with lung adenocarcinoma, a kind of cancer that does not affect the digestive tract.

In this study, we aimed to introduce LFEPT into the prevention and treatment of CINV caused by cisplatin to explore its clinical application effect in patients with lung adenocarcinoma.

2. Materials and Methods

2.1. Patients

Eighty-two patients with lung adenocarcinoma who received cisplatin-based chemotherapy in our hospital from January 2019 to December 2019 were selected as the research subjects. By random numerical table method, all included patients were randomly divided into an experimental group (n=41) and a control group (n=41). The experimental group was treated with LFETP combined with 2 antiemetic drugs (tropisetron hydrochloride and dexamethasone), while the control group was treated with the same 2 antiemetic drugs. The study was approved by the Ethics Committee of Wuhan Central Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan Central Hospital, and all subjects signed informed consent before receiving treatment.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) patients with lung adenocarcinoma clearly diagnosed by pathology or cytology need combined chemotherapy; (2) 18–60 years old, expected survival time ≥3 months; (3) Karnofsky Performance Status (KPS) score ≥60; (4) the results of electrocardiogram, blood routine, liver, kidney function, and blood glucose were normal before chemotherapy; (5) no intracranial pressure increase, intestinal obstruction, or gastrointestinal diseases caused by intracranial vomiting; (6) no vomiting within 24 hours and no antiemetic drugs were used; (7) all the enrolled patients signed informed consent and were willing to accept the treatment protocol. Exclusion criteria: (1) severe cardiopulmonary dysfunction, abnormal blood routine, liver and kidney function that unable to tolerate chemotherapy; (2) patients with gastrointestinal reactions caused by other chemotherapy drugs; (3) patients with brain metastases; (4) those patients who have not signed the informed consent and are unwilling to accept the treatment protocol. Discontinuation criteria: (1) patients could not tolerate the experiment; (2) the curative effect cannot be determined if the treatment is not completed according to the prescribed course of treatment; (3) serious adverse events or special changes occurred during treatment.

2.3. Methods

All enrolled patients were treated with the regimen of Pemetrexed (500 mg/m^2) + Cisplatin (75 mg/m^2) for 6 consecutive cycles. Control group: Tropisetron hydrochloride 5 mg + normal saline 100 mL, intravenous drip; Dexamethasone 5 mg+10 mL normal saline was injected intravenously, once a day 30 minutes before chemotherapy. Experimental group: The 2 drugs were used the same as controls. Besides, Neiguan acupoint was stimulated percutaneously before each chemotherapy by the LFEPT device. Electrical stimulation was given for 1–2 hours before each chemotherapy. The operator put the circular self-adhesive electrodes with a diameter of 3 cm connected to the electrical stimulation instrument on both sides of the Neiguan acupoint (the left side is connected to the positive electrode, and the right side is connected to the negative electrode) to adjust the frequency to 4 Hz. The current intensity was within the range of 3–15 mA and adjusted to the maximum degree that patients could comfortably tolerate, and the duration was 30 min. The acupoint stimulation equipment used is a G9805-C low-frequency electric pulse therapy instrument (Shanghai Medical Equipment High-tech Company, Shanghai, China). The nurses in the ward did not have any acupuncture or TCM background, but they were all trained in acupuncture points of TCM.

2.4. Evaluation criteria

On the 1st to 6th day of chemotherapy, the R-INVR scale[12] and Functional Living Index Emesis (FLIE) questionnaire[13] were used to evaluate symptoms and quality of life, respectively. The R-INVR evaluation scale was filled every 24 hours to record the frequency, intensity, and duration of nausea, dry retching, and vomiting. R-INVR scale is an internationally used vomiting assessment scale and its reliability and validity have been confirmed, which includes 8 items and can be divided into 3 dimensions: (1) the time component of symptom experience; (2) symptom frequency component; (3) symptom severity component. Each dimension has different items and different scores corresponding to the 3 symptoms. Likert 0–4 scoring method was adopted for the scale. 0–4 points respectively represented "none", "some", "moderate", "very obvious" and "very severe and unbearable". The minimum score is 0 and the maximum score is 32. The higher the score of each dimension, the more serious nausea and vomiting of the patient. Validity: Ranks 0 and 1; Effective rate = effective cases/total cases × 100%.[12] FLIE scores were calculated using specialized measures and statistical methods to assess the impact of acute nausea and vomiting within 48 hours after chemotherapy and delayed nausea and vomiting within 6 days after chemotherapy on patients' quality of life. The Cronbach a-α coefficient of the FLIE scale was 0.79, and the structural validity was 0.74–0.97. Each dimension of the scale included 9 items, including severity, diet, daily social interaction, recreational activities, degree of distress, daily function, and housework ability, and there were 2 dimensions of nausea and vomiting. Each item was scored on a Likert scale of 0 to 7. The higher the score, the less impact it had on the quality of life. In contrast, the lower the score, the associated negative impact of CINV on patients' lives.[13]

2.5. Statistical analysis

Statistical analysis was performed using Statistical Product and Service Solutions software (SPSS 22.0, Inc., Chicago, USA). The results were presented as mean ± standard deviation (SD), and Student's *t*-test was applied for continuous data. While Chi-square test for categorical data. A value of $P<.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of two groups

There were no statistically significant differences in age, gender, clinical stage, KPS score, history of anxiety, and history of motion sickness between the 2 groups (all $P>.05$, respectively; Table 1).

Table 1

Comparison of baseline data between the 2 groups

Item		Control (n=41)	Experimental (n=41)	Statistic value	*P* value
Age (y)		56.41 ± 9.22	55.52 ± 7.02	t=1.99	.62
Gender	Male	34	36	χ^2=0.39	.76
	Female	7	5		
Stage	II	25	28	χ^2=0.48	.65
	III–IV	16	13		
Anxiety	Present	31	27	χ^2=0.94	.47
	Absent	10	14		
Motion sickness	Present	28	24	χ^2=0.84	.49
	Absent	13	17		
KPS score	70–80	15	13	χ^2=0.22	.82
	80–90	26	28		

Table 2

Comparison of nausea between the 2 groups

		Degree of nausea reaction							
Time	Group	0	I	II	III	IV	Effective rate (%)	Statistic value	*P* value
Day 1	Control	43	141	39	18	5	74.80	0.51	.54
	Experimental	39	138	39	24	6	71.95		
Day 2	Control	55	141	29	15	6	79.67	5.97	.015
	Experimental	63	153	21	6	3	87.80		
Day 3	Control	56	151	18	14	7	84.15	6.15	.013
	Experimental	61	164	10	6	5	91.46		
Day 4	Control	51	154	19	18	4	83.33	7.38	.01
	Experimental	66	159	9	6	6	91.46		
Day 5	Control	57	150	21	14	4	84.15	4.72	.03
	Experimental	60	163	9	7	6	90.65		

3.2. Comparison of nausea rates between the two groups

The effective rates of preventing nausea in the trial group from day 1 to day 5 after chemotherapy were 71.95%, 87.80%, 91.46%, 91.46%, and 90.65%, respectively. In the control group, the effective rates of preventing nausea on the 1st to 5th day after chemotherapy were 74.80%, 79.67%, 84.15%, 83.33%, and 84.15%, respectively. Statistical analysis showed that except for the 1st day, the effective rates of preventing nausea in the 2–5 days in the experimental group were significantly higher than that in the control group (P < .05, respectively; Table 2).

3.3. Comparison of dry retching rates between the two groups

The effective rates of preventing dry retching in the experimental group from day 1 to day 5 after chemotherapy were 88.21%, 33.74%, 37.80%, 84.15%, and 90.65%, respectively. By contrast, the effective rates of preventing dry retching in the control group were 86.99%, 24.80%, 28.86%, 74.80%, and 84.96% from day 1 to day 5 after chemotherapy, respectively. Statistical analysis showed that except for the 1st day, the effective rates of prevention of dry retch in the experimental group were significantly higher than that in the control group on the other 4 days (all P<.05, respectively; Table 3).

3.4. Comparison of vomiting rates between the two groups

The effective rates of preventing vomiting in the experimental group from day 1 to day 5 after chemotherapy were 84.96%, 61.79%, 54.47%, 56.91, and 71.14%, respectively. In the control group, the effective rates of preventing vomiting from day 1 to day 5 after chemotherapy were 80.89%, 50.00%, 43.50%, 41.87%, and 60.98%, respectively. Except for no significant difference in the effective rates between the 2 groups on day 1, the effective rates of preventing vomiting in the experimental group on the other 4 days were significantly higher than that in the control group (all P<.05, respectively; Table 4).

3.5. Comparison of functional index between the two groups

Life function indexes of the 2 groups were compared on day 1 and day 6 after chemotherapy. The score of FLIE had no difference between the 2 groups on the first day after chemotherapy (84.05 vs 82.69, P=.30), and the score was significantly higher in the experiment group on day 6 compared with the control group (103.71 vs 89.38, P=.02). (Table 5).

3.6. The side effects after treatment

Adverse events were measured 5 days after the intervention, the experimental group had significantly less constipation, stomach pain, and abdominal distension than the control group (P<.05), while the difference in the incidence of loss of appetite between the 2 groups was not statistically significant (P>.05) (Table 6).

4. Discussion

Nowadays, great progress has been made in the research and clinical application of antiemetic drugs.[5] At present, 5-hydroxytryptamine (5-HT_3) receptor antagonist combined with dexamethasone is mostly used in chemotherapy to prevent vomiting, which has good efficacy for one-way chemotherapy or acute vomiting, but it has poor efficacy for vomiting caused

Table 3

Comparison of dry retching between the 2 groups

Time	Group	Degree of dry retching					Effective rate (%)	Statistic value	*P* value
		0	I	II	III	IV			
Day 1	Control	144	70	21	8	3	86.99	0.17	.79
	Experimental	148	69	16	11	2	88.21		
Day 2	Control	18	43	105	46	34	24.80	4.75	.03
	Experimental	23	60	110	41	12	33.74		
Day 3	Control	17	54	127	34	14	28.86	4.44	.04
	Experimental	21	72	119	21	13	37.80		
Day 4	Control	52	132	37	13	12	74.80	6.59	.01
	Experimental	66	141	15	16	8	84.15		
Day 5	Control	47	142	29	15	13	76.83	5.26	.03
	Experimental	60	149	19	7	11	84.96		

Table 4

Comparison of vomiting between the 2 groups

Time	Group	Degree of vomiting					Effective rate (%)	Statistic value	*P* value
		0	I	II	III	IV			
Day 1	Control	147	52	21	14	12	80.89	1.44	.28
	Experimental	156	53	16	19	2	84.96		
Day 2	Control	51	72	89	18	16	50.00	6.93	.01
	Experimental	63	89	72	13	9	61.79		
Day 3	Control	25	82	102	17	20	43.50	5.93	.02
	Experimental	22	112	89	18	5	54.47		
Day 4	Control	14	89	107	24	12	41.87	11.13	.00
	Experimental	36	104	52	40	14	56.91		
Day 5	Control	29	121	51	35	10	60.98	5.67	.02
	Experimental	39	136	29	27	15	71.14		

Table 5

Comparison of life function indexes between the 2 groups

	Control	Experimental	Statistic value	*P* value
Day 1	82.69 + 24.78	84.05 ± 26.93	1.18	.30
Day 6	89.38 ± 19.29	103.71 ± 27.18	1.98	.02

Table 6

Comparison adverse events rate after chemotherapy in the 2 groups

Group	N(%)	Constipation	Abdominal pain	Abdominal distension	Loss of appetite
Control group	41	17(42)	10(24)	13(32)	12(30)
Experimental group	41	9(22)	3(8)	6(14)	6(14)
$\chi 2$		4.596	4.762	4.574	3.73
P		.031	.028	.032	.053

by multi-course chemotherapy or cisplatin and other drugs.[14] Although a new generation of NK-1 receptor antagonists can reduce the incidence of CINV, it may still occur in some malignant tumor patients.[15] Previous prospective studies showed that 34% of patients developed acute CINV, while 58% of patients developed delayed CINV after chemotherapy.[16] Therefore, it is important to reduce the incidence of CINV for improving patients' clinical treatment compliance and quality of life.

The mechanism of CINV is very complex and current studies demonstrated that chemotherapy drugs can cause vomiting through central and peripheral pathways.[17] As cytotoxic drugs, chemotherapy drugs can stimulate intestinal pheochromocytes in the gastrointestinal mucosa to secrete 5-HT_3, which stimulates the vagus nerve to the brain stem and then stimulates the vomiting center by binding with the 5-HT_3 receptor, thereby causing vomiting.[14] Acute CINV usually starts 2 hours after chemotherapy and reaches its peak 4–6 hours after chemotherapy, while delayed CINV occurs 1–5 days after chemotherapy, which is often related to the use of cisplatin and is difficult to control with current antiemetic drugs.[18] At present, several societies recommend a triple anti-vomiting regimen (5-HT_3 receptor antagonist+dexamethasone+NK-1 receptor antagonist) as the first-line treatment for the prevention of acute stage CINV caused by highly emetogenic chemotherapy. However, adherence to the guidelines remains low in clinical practice.[5,6] A study from a community hospital in the United States confirmed that only 57% of patients received treatment regimens consistent with the guidelines for CINV.[19] Newer drugs such as NK-1 receptor antagonists and palonosetron have better preventive effects on acute and delayed vomiting, but they are more expensive and have side effects such

as elevated transaminase, constipation, and headache. In addition, glucocorticoids are also one of the main drugs for the prevention of CINV. However, current studies have reported that glucocorticoids may cause side effects such as drowsiness, appetite, weight gain, and gastrointestinal symptoms.[20] Therefore, there is an urgent need for new treatments to reduce the incidence of CINV and improve patient compliance, to improve the treatment efficiency of patients.

According to TCM, chemotherapy-induced nausea and vomiting are caused by chemotherapy drugs that damage the spleen and stomach, weaken the spleen and stomach, weaken the stomach, disharmony between the spleen and stomach and reverse the stomach qi, and the treatment is based on the principle of reversing the stomach.[8] At present, TCM therapy has definite curative effects on the treatment of CINV, such as acupuncture, acupoint injection, acupoint application, acupoint massage, and moxibustion, which have obvious effects on alleviating gastrointestinal reactions after chemotherapy.[8] Numerous studies have reported the effectiveness of acupuncture in the treatment of CINV.[12] However, acupuncture requires a high level of experience on the part of the operator, and may cause pain and even rejection. Therefore, it is urgently needed in clinical practice to stimulate the relevant acupoints with a noninvasive and convenient therapy to replace the effect of acupuncture treatment. Low-frequency electric pulse therapeutic instrument is an external transcutaneous nerve electrical stimulation therapeutic instrument. By sending out a specific frequency of low-frequency pulse, stimulation of Neiguan acupoints can inhibit and reduce the incidence of nausea and vomiting. In addition, nurses without any acupuncture or TEM background can safely carry out treatment after simple training. Studies have reported that it is effective in the prevention of nausea and vomiting for patients with gastric cancer after chemotherapy.[11] In the present study, the results showed that the use of an LFEPT device combined with antiemetic agents (tolisetron hydrochloride and dexamethasone) can significantly improve the effectiveness of prevention of nausea, retching, and vomiting on days 2–5 after chemotherapy, and significantly improve the life function index of patients after chemotherapy. It also has been confirmed that combined administration ($5\text{-}HT_3$ receptor antagonist + dexamethasone) + LFEPT can reduce the incidence of delayed CINV, improve the completion rate of full-course chemotherapy, improve the cure rate of tumor chemotherapy, and prolong the overall survival of patients.

This study has the following shortcomings: (1) small sample size; (2) short observation time; (3) included subjects were only patients with lung adenocarcinoma, and the efficacy of this therapy in these cancer types still needs to be further studied. Therefore, the sample size, the scope of inclusion, and the duration of the study can be further expanded in the future, and the application value of low-frequency electric pulse therapy in the prevention of chemotherapy-induced nausea and vomiting can also be further explored.

5. Conclusion

Taken together, our results show that low-frequency electric pulse therapy can not only significantly ameliorate nausea, retching, and vomiting of patients after chemotherapy but also improve the quality of life of patients after chemotherapy, which is worthy of clinical promotion and application.

Author contributions

Conception and design: Yonghong Han.
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Manuscript writing: All authors.
Final approval of manuscript: All authors.
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