Effect of low-frequency electrical acupoint stimulation on nausea and vomiting in NSCLC patients receiving highly emetogenic regimens

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Research Article

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Abstract

**Purpose:** To assess the efficacy and tolerability of low-frequency electrical acupoint stimulation plus standard antiemetics following highly emetogenic chemotherapy in patients with non-small cell lung cancer (NSCLC).

**Methods:** NSCLC patients who received highly emetogenic chemotherapy were randomized into control and observation groups by random number table. Patients in the observation group received the triple antiemetic regime plus low-frequency electrical acupoint stimulation (since the day of chemotherapy for 5 days consecutively). Meanwhile, those in the observation group only received the triple antiemetic regime. The severity of nausea and vomiting episodes were recorded on a daily basis. On the sixth day after chemotherapy, the patients were scored by the Functional Living Index Emesis (FLIE) questionnaire. The complete response rate of vomiting, incidence of nausea, severity of nausea, and FLIE score were compared between the two groups.

**Results:** Compared with the control group, the incidence of nausea decreased significantly in the observation group throughout the course of treatment (66.7% vs. 40.5%, \( p=0.016 \)). At 24-120h after chemotherapy, the complete response rate of vomiting at the delayed stage increased conspicuously in the observation group (88.1% vs. 69.1%, \( p=0.033 \)). At this stage, the proportion of patients without nausea in the observation group was also significantly higher (73.8% vs. 47.6%, \( p=0.014 \)). The total FLIE scores in the observation group were conspicuously higher than the control group (106.05±15.35 vs. 95.04±20.02, \( p=0.02 \)).

**Conclusion:** The combination of the triple antiemetic regimen and low-frequency electrical acupoint stimulation memorably improves chemotherapy-induced nausea and vomiting in NSCLC patients.

1 Introduction

Although targeted therapy and immunotherapy have revolutionized cancer treatment, chemotherapy is still the cornerstone of advanced cancer treatment. Chemotherapy-induced nausea and vomiting (CINV) is one of the common gastrointestinal side effects of chemotherapy. CINV can lead to dehydration, metabolic disorders, nutritional disorders and weight loss, which can have a substantial negative impact on patients’ mood, physical function and treatment effectiveness. Because of the decline of quality of life caused by CINV, patients with malignant tumor are more likely to show a decline in compliance with follow-up chemotherapy, or even give up chemotherapy completely, which further affects the overall survival rate.

The standard first-line chemotherapy regimens for most patients with non-small cell lung cancer (NSCLC) contain platinum, though both cisplatin and carboplatin (AUC \( \geq 4 \)) are highly emetogenic chemotherapy (HEC). The antiemetic guidelines of HEC regimen usually recommend a triple antiemetic regimen consisting of 5-HT3 receptor antagonist, neurokinin-1 receptor antagonist and dexamethasone, or a
quadruple antiemetic regimen consisting of the above three drugs plus olanzapine. Despite the use of triple or quadruple antiemetic regimen, there are still more than a quarter of chemotherapy patients suffering from vomiting. It has been reported that 52% of patients suffer nausea despite taking antiemetics. Up to now, little is known about the pathogenesis of nausea in modern medicine. As a subjective feeling, nausea is usually considered to be caused by the stomach and occurs before vomiting. How to control CINV remains a challenge in cancer treatment.

According to the theory of traditional Chinese medicine, stimulating acupoints along meridians can relieve the symptoms of some diseases. Traditional acupuncture is an invasive technique that involves inserting fine needles into selected acupuncture to achieve therapeutic effect. P6 point, also known as Neiguan point or G-Jo point, is located on the anterior forearm, two cun proximal to the distal wrist crease (equivalent to the width of a thumb), between the tendons of palmaris longus and flexor carpi radialis muscles. It is believed that Acupuncture at P6 point can reduce the incidence and severity of postoperative nausea, vomiting, morning sickness and CINV. ReliefBand is a wearable anti-nausea wristband designed according to the principles of transcutaneous electrical nerve stimulation (TENS) and the theory of the Chinese traditional meridian and acupoint. Approved by Food and Drug Administration in 2000, ReliefBand is now widely used to alleviate morning sickness, motion sickness, and vomiting after surgery and CINV by worn on the wrist to stimulate Neiguan point. However, few studies have studied whether the combination of the triple antiemetic regimen and the low-frequency electrical acupoint stimulation can further ameliorate CINV. Therefore, we aimed to assess the antiemetic effect and safety of the combination therapy following highly emetogenic chemotherapy in NSCLC patients.

2 Patients And Methods

2.1 Patients

This retrospective clinical study was approved by the ethics committee of Peking University International Hospital. NSCLC patients receiving highly emetogenic chemotherapy at the Peking University International Hospital from December 1, 2019 to December 30, 2022 were collected. They were randomized into control and observation groups by random number table. Patients in the observation group received the triple antiemetic regime plus low-frequency electrical acupoint stimulation (since the day of chemotherapy for 5 days consecutively). Meanwhile, those in the observation group only received the triple antiemetic regime. Inclusion criteria: (1) patients having been histopathologically or cystologically confirmed with NSCLC; (2) receiving a single dose of highly emetogenic chemotherapy (cisplatin or carboplatin AUC ≥ 4); (3) aged 18 and above; (4) Eastern Cooperative Oncology Group (ECOG) PS score 0–1; (5) life expectancy over 3 months; (6) normal heart, liver, kidney and other major organs function; (7) volunteered to participate in this study and signed informed consent. Exclusion criteria: (1) patients with severe cardiac, renal, and hepatic insufficiency; (2) wearing a pacemaker and other medical electronic devices; (3) metal allergy; (4) not capable of signing informed consent; (5) nausea, vomiting or taking antiemetic drugs 24 h before chemotherapy; (6) concurrent radiotherapy.
2.2 Treatment

All patients received prophylactic antiemetic therapy according to the guidelines before chemotherapy, which consisted of intravenous injection of ondansetron (8 mg d1-d4), intravenous injection of dexamethasone (5 mg d1, 3 mg d2-d4), and oral aprepitant (120 mg d1, 80 mg d2-d3). Patients in the observation group wore the low-frequency electrical acupoint stimulation from 30 min before chemotherapy to 5 days after chemotherapy. The control group only received standard antiemetics. The low-frequency electrical acupoint stimulation was provided by Nasi Kefeng (Dalian) Medical Technology Co., Ltd. (Dalian, China). One researcher instructed the patients how to wear the stimulator, that is, by attaching two metal electrodes attached to the inner surface of the wrist at P6 acupoint, as mentioned above. The patients were told that it was normal if there was mild tingling sensation in the wrists. The patients were asked to wear the low-frequency electrical acupoint stimulator for 5 consecutive days except when bathing.

2.3 Data collection

(1) The risk of vomiting was assessed before chemotherapy. The contents of assessment included age, gender, history of pregnancy and morning sickness, and history of alcohol consumption. (2) Patients were asked to log themselves within five days of wearing the stimulator. (3) The incidence and severity of vomiting and nausea and the use of rescue drugs within 0-120 h were recorded. (4) The severity of nausea was assessed using the 10 cm horizontal visual analog scale, where a mark made at 0 cm represented "No nausea at all" and 10 cm "Extreme nausea". Any mark made beyond 5 mm represented the presence of nausea, and that beyond 2.5 cm severe nausea. (5) The Functional Living Index-Emesis (FLIE) questionnaire was administered to patients on the last day of the study\textsuperscript{11}. A healthcare worker was assigned with the task of following up the patients every day and keeping daily records.

2.4 Evaluating indicators

The indicators between two groups were compared in the following indicators, including complete response rate of vomiting (no vomiting at all and without the use of any rescue drugs), incidence of nausea, incidence of severe nausea, adverse events, and FLIE score at the acute and delayed stages and throughout the course of treatment.

2.5 Statistical analysis

SPSS 26.0 software was used to process the data. If the quantitative data accorded with normal distribution, it was expressed as mean ± standard deviation (SD). If it did not conform to the normal distribution, it was expressed as the median (quartile spacing) [M(QR)]. Qualitative data were expressed in frequency and percentage (%). Rates and percentages were compared between the two groups using the Wilcoxon rank sum test and Fisher's exact test. A \( p < 0.05 \) was statistically significant.

3 Results
3.1 Patient characteristics

A total of 184 NSCLC patients were included. The baseline characteristics in the two groups were showed in Table 1. The median age was 63.8 and 64.7 years in the observation and control groups, respectively. There were 68 males and 24 females in the observation group, while 65 males and 27 females in the control group. In addition, there were no significant differences in the smoking history, history of alcohol consumption, history of motion sickness, history of pregnant vomiting, pathological type and chemotherapy regimens ($p < 0.05$). The male patients and the adenocarcinoma patients accounted for a greater proportion.
Table 1  
Baseline characteristics of the two groups of patients

<table>
<thead>
<tr>
<th>Items</th>
<th>Observation group (n = 92)</th>
<th>Control group (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>63.8</td>
<td>64.7</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Smoking history</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td>History of alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>No</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>History of motion sickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>History of pregnant vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Pathological types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
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<td></td>
</tr>
<tr>
<td>Cisplatin-containing</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Carboplatin-containing</td>
<td>69</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviation: n, number of patients
Table 2
Summary of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Observation group (n = 92)</th>
<th>Control group (n = 92)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>16(17.4%)</td>
<td>15(16.3%)</td>
<td>0.844</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>12(14.1%)</td>
<td>23(22.8%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hiccups</td>
<td>7(7.6%)</td>
<td>8(8.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3(3.3%)</td>
<td>4(4.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9(9.8%)</td>
<td>7(7.6%)</td>
<td>0.601</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2(2.2%)</td>
<td>1(1.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Abbreviation: n, number of patients

<sup>a</sup>P values were calculated with the Fisher's exact test or the chi-square test.

4 Discussion

We found that the low-frequency electrical acupoint stimulation could dramatically reduce the incidence of CINV, especially at the delayed stage, which can be used in combination with the triple antiemetic regimen. Along with development of antiemetics and the increase of clinical application, CINV is now put under control in most chemotherapy patients. Nevertheless, some cancer patients are still suffering from CINV, especially those treated with the HEC regimen<sup>12</sup>. In the present study, we showed that the low-frequency electrical acupoint stimulation could dramatically reduce the incidence of nausea throughout the course of treatment and the incidence of nausea at the delayed stage. The incidence of nausea did not differ significantly whether low frequency electrical acupoint stimulation is applied or not at the acute stage. Traditional Chinese medicine can deliver definite efficacy for CINV, including acupuncture, acupoint injection, acupoint paste, acupoint massage, and moxibustion<sup>13</sup>. All these therapies can relieve the gastrointestinal reactions after chemotherapy<sup>14</sup>. Many studies have reported the efficacy of acupuncture in CINV<sup>15</sup>. However, acupuncture is an invasive procedure and may cause complications such as pain and infections. This procedure cannot be administered unless by experienced acupuncturists. There is an urgent need to develop a non-invasive and convenient method for acupoint stimulation. Electrical stimulation of the P6 acupoint has proven efficacy in controlling CINV<sup>16</sup>. ReliefBand, the low-frequency electrical acupoint stimulator used in the present study, is a medical device that can be worn on the wrists after simple instructions from the healthcare workers. This device is easy to use in a clinical setting. We also found that the combination of the triple antiemetic regimen and ReliefBand effectively reduced the incidence of nausea in NSCLC patients caused by HEC throughout the course of treatment and at the delayed stage.
antiemetic regimen significantly reduced the incidence of vomiting in patients treated with the HEC regimen, over one-half of the patients still had nausea, which shorted the patients' life quality. ReliefBand was proven effective in meeting the clinical needs of cancer patients in this study, but more prospective studies should be conducted with a larger sample size in the future. The decreasing trend in the incidence of nausea at the acute stage, however, did not show a significant difference between the two groups, which might be attributed to the small sample size.

Our study also indicated a significant difference in the complete response rate of vomiting at the delayed stage between the two groups. This finding confirmed the effectiveness of ReliefBand in controlling CINV. The complete response rate of vomiting throughout the course of treatment and at the acute stage were not significantly different between the two groups. However, these two indicators were both improving in the observation group. The lack of statistical significance might be also related to the small sample size. The mechanism underlying the antiemetic effect of stimulation of the P6 acupoint is not yet fully understood. According to a previous study, the pulse signals emitted by the low-frequency electrical acupoint stimulation are transmitted to the cerebral cortex via the nervous system to control CINV. According to others, electrical stimuli delivered to the internal and external cutaneous nerves of forearm through electrical stimulation of the P6 acupoint are further transmitted to the C5 spinal cord. Such stimuli can activate the phrenic nerve to reduce vomiting. Importantly, the mechanism of P6 acupoint electrical stimulation remains to be further studied.

The FLIE score in the observation group was significantly increased compared with the control group, which might be related to the decreased incidence of nausea and vomiting. There was no significant difference in the incidence of adverse reactions between the two groups, indicating that it was safe and feasible to wear the electrical acupoint stimulator.

The present study also has the following shortcomings. First, the study is retrospective in nature and may contain selection biases. Second, the sample size is small, which might affect its statistical value. Third, we do not discuss the mechanism of the electrical acupoint stimulating in improving CINV. We will further expand the sample size for prospective randomized clinical trials to verify the antiemetic effect of the electrical acupoint stimulation.

5 Conclusion

In conclusion, low-frequency electrical acupoint stimulation plus triple antiemetic regimen could dramatically reduce the incidence of nausea throughout the course of treatment and the incidence of nausea at the delayed stage. Besides, the combination therapy increases the complete response rate of vomiting at the delayed stage, thereby improving the life quality of patients receiving chemotherapy. Low-frequency electrical acupoint stimulation is worthy of further popularization as a complement to the triple antiemetic regimen.

Declarations
Authors' contributions

Jun Liang, and Chuanhao Tang conceived and designed the study. Xiangyi Wang and Xing Wei collected and analysed the data. Li Lin was involved in the preparation of tables and figures. Lingling Zhang and Xing Wei drafted the manuscript. All authors read, critically revised, and approved the manuscript.

Conflict of interest

No conflicts of interest

Acknowledgements

None

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References


Figures
Figure 1

No nausea rate at different stage: whole course (66.7% vs. 40.5%, p=0.016); acute stage (76.2% vs. 59.5%, p=0.102); delayed stage (73.8% vs. 47.6%, p=0.014);*: P < 0.05
Figure 2

**Complete response rate at different stage:** whole course (83.3% vs. 66.5%, \( p = 0.078 \)); acute stage (90.5% vs. 85.7%, \( p = 0.500 \)); delayed stage (88.1% vs. 69.1%, \( p = 0.033 \));

*: \( P < 0.05 \)