Transcutaneous Acupoint Electrical Stimulation on Chemotherapy-Induced Constipation for Non-Small Cell Lung Cancer Patients: A Randomized Controlled Trial

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Received: April 21, 2020; Accepted: November 30, 2020; Published: March 12, 2021

Objective: Chemotherapy-induced constipation (CIC) adversely affects the quality of life of non-small cell lung cancer (NSCLC) patients. This study aimed to investigate the clinical effects of transcutaneous acupoint electrical stimulation (TAES) on CIC. Methods: Sixty NSCLC patients who received chemotherapy at Hunan Cancer Hospital, Changsha, China, were assigned to the TAES (n = 30) or control (n = 30) group using Research Randomizer. In the TAES group, four acupoints, namely Tianshu, Quchi, Zusanli, and Shangjuxu, were stimulated six times a week, lasting for 4 weeks, while the control group received the usual care. The Bristol Stool Form Scale (BSFS) and the Constipation Assessment Scale (CAS) were used. Results: Both the BSFS and CAS scores for the experimental group were significantly higher than that for the control group (P = 0.004 and P < 0.001 separately). Conclusions: TAES was effective for alleviating constipation in NSCLC patients receiving chemotherapy and was a safe and practical nursing intervention.

Key words: Chemotherapy-induced constipation, non-small cell lung cancer patients, transcutaneous acupoint electrical stimulation

ABSTRACT

Introduction

Lung cancer is the most common type of cancer and the leading cause of cancer death in China.[1] Approximately 75%–85% of all lung cancers are non-small cell lung cancer (NSCLC).[2] It has become standard procedure for NSCLC patients to receive adjuvant chemotherapy after radical surgery, leading to a 5-year survival rate increase from 54% to 69%. However, the complications induced by chemotherapy are still a concern and may cause physical and psychological symptoms, thus decreasing

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Cite this article as: Mao T, Liu X, Cheng Q, Chen Y. Transcutaneous Acupoint Electrical Stimulation on Chemotherapy-Induced Constipation for Non-Small Cell Lung Cancer Patients: A Randomized Controlled Trial. Asia Pac J Oncol Nurs 2021;8:385-92.
the treatment compliance rates of patients. Therefore, the National Cancer Center advocates for the focus by medical staff on the reduction of pain and other symptoms while increasing NSCLC patients’ quality of life (QOL). Although chemotherapy contributes to prolonging life, it is accompanied by side effects like gastrointestinal (GI) symptoms (constipation, nausea, and vomiting). These adverse reactions reduce total food intake, decrease the activity levels of patients, and cause constipation. Another reason for the occurrence of constipation is the increased use of antiemetic drugs and pain relievers. According to a recent study, cancer patients receiving chemotherapy may suffer from constipation at an incidence rate as high as 50%–80.

Transcutaneous acupoint electrical stimulation (TAES) is an electrical stimulation method that sends electrical impulses into acupoints through electrodes on the skin’s surface. It has the same effect as electroacupuncture which relieves constipation symptoms caused by oral intake of morphine sulfate by cancer patients. According to the theory of Traditional Chinese Medicine (TCM), TAES Tianshu (ST25), Quchi (LI11), Zusanli (ST36), and/or Shangjuxu (ST37) may be favorable for the improvement of constipation. The combined effects of these four acupoints on constipation symptoms in cancer patients undergoing chemotherapy have not been reported yet, and the literature indicates no incompatibility among them. This study aimed to fill this void by investigating the effects of TAES on constipation for NSCLC patients undergoing chemotherapy.

**Constipation and transcutaneous acupoint electrical stimulation**

Constipation is a distressing, continual, and underestimated complication experienced by cancer patients. Chemotherapy-induced constipation (CIC) is different from general constipation, mainly because it can be predictable. The mechanisms of CIC are poorly defined in clinical research. Constipation in cancer patients is often caused by drugs that are given to control other chemotherapy- or cancer-induced symptoms (such as antiemetics for nausea and vomiting and opioids for pain) and the chemotherapeutic agents themselves. Chemotherapy-induced loss of appetite, anxiety, electrolyte disorders, and vomiting can also lead to CIC.

The GI tract is innervated by the enteric nervous system together with fibers from extrinsic sympathetic, parasympathetic (vagus nerve), and sensory afferent neurons. The nerve cells in the intestines include the submucosal plexus and the myenteric plexus. These two groups of nerve cells are the major components of the enteric nervous system and integrate the motor and secretory activities of the GI tract. Chemotherapy drugs have clear toxic effects on autonomic nerves that govern intestinal peristalsis and nerve cells in the intestines, which can cause gastric emptying and intestinal motility disorders. A secondary reason for CIC is attributed to the natural course of the disease, which causes intestinal obstruction and impedes metabolic function which may result in dehydration and electrolyte imbalance, thus causing constipation. Finally, a decrease in fiber and liquid consumption as well as a decrease in physical activity can also lead to constipation.

Many methods exist for the treatment of constipation, including increased physical activity and high intake of fiber and fluids. However, these approaches often take a long time to have any positive effect, and patient compliance is usually low. Medical intervention relies mainly on medicine administration, but frequent use of laxatives may cause malabsorption of other drugs and can even worsen constipation by causing normal intestinal reaction change and weakened muscle tension. Therefore, more effective interventions are essential for the alleviation of CIC.

TAES incorporates the use of electrodes into traditional Chinese acupuncture therapy to stimulate specific acupuncture points in order to relieve symptoms. As a noninvasive method, TAES could easily be applied to cancer patients without causing them any pain. It causes no adverse reactions such as those that may be caused by acupuncture needles. Prior studies have shown that TAES may adjust autonomic balance by enhancing vagal activity and suppressing sympathetic activity.

TAES combines percutaneous nerve electrical stimulation with acupuncture points based on the theory of TCM. According to a study on the effects of percutaneous tibial nerve stimulation in alleviating slow-transit constipation in patients, the treatment group that received percutaneous tibial nerve stimulation experienced improvement of their constipation symptoms and Patient Assessment of Constipation (PAC) QoL scores also improved.

In addition, a study conducted on chronic constipation in which electrical stimulation was applied to the experimental group, while a sham stimulation was used in the placebo-controlled group, found that PAC Symptoms Questionnaire and PAC-QoL scores significantly increased for participants in the experimental group. However, no research has reported the improvement of constipation in cancer patients undergoing chemotherapy through the application of TAES. Therefore, this study attempted to examine the effects of TAES on constipation among lung cancer patients receiving chemotherapy. Accordingly, the results will be used as the basic criteria for developing nursing interventions in clinical settings.
Methods

Design and sample

This study followed a randomized controlled trial design. Two researchers were responsible for patient recruitment and random allocation and were blinded to group allocation. Using Research Randomizer (version 4.0) (Urbania and Plous) to produce a random number between 1 and 62 and create a table, patients were randomly divided either into the TAES or control group, with 31 cases in each group. Participants were patients who had been diagnosed with NSCLC and were receiving chemotherapy at Hunan Cancer Hospital, China. The study was conducted from October to December 2018.

The inclusion criteria were as follows: (a) patients with NSCLC aged 18 years and above who experienced constipation after chemotherapy, (b) scored more than 60 points on the Karnofsky Performance Score (KPS) (Karnofsky), and (c) gave informed consent. Exclusion criteria consisted of psychiatric disease, the presence of lesions inside the intestine, and having undergone an abdominal operation in the past 6 months. To determine the number of participants, G* Power 3.10 (Heinrich Heine Universitat, Dusseldorf, Germany) was used, with the suggested Cohen significance level (α) at 0.05 and the test power 1−β at 0.8. Ten participants (5 in each group) were included in the preliminary experiment. According to the preliminary experiment results, the mean values of the Constipation Assessment Scale (CAS) in the experimental and control groups were 5.4 and 4.4, respectively, within each group was 1.095. Based on the above results, the effect size was calculated as 0.456621 and thus the calculated sample size was at least 40 participants. To provide for the potential 20% nonresponse rate, a minimum of 48 participants were recruited.

Measures

Demographic and disease-related characteristics included age, marital status, activity level, number of meals, cycle and protocol of chemotherapy, and the stage of cancer. Outcomes were measured with the Bristol Stool Form Scale (BSFS) and the CAS.

The CAS was developed by Agachan et al. and translated and validated by McMillan and Williams. The CAS includes eight items, with scores ranging from 0 to 3. Higher scores reveal severe constipation. In McMillan’s study, reliability was assessed as Cronbach’s alpha at 0.70. The BSFS was developed by Heaton et al. and is classified into 1–7 points to measure stool form in clinical practice and research. A score of 1–2 points indicates constipation, 3–4 points indicates normal feces, and 5–7 points indicates diarrhea. In the study by Chumpitazi et al., reliability was assessed with intraclass correlations of 0.88.

Intervention

The experimental group received TAES for a period of 4 weeks. GI–I middle/low-frequency therapeutic apparatus (Beijing Simailaifu Medical Equipment Technology Co. Ltd., Beijing, China) was used for TAES. For stimulation, 2 kHz modulated medium-frequency current and 1–150 Hz modulation frequency were used. In a study of therapeutic observation of TAES for constipation during chemotherapy for breast cancer implemented by Yang et al., the period of intervention was 3 days. In an assessment of the literature regarding acupuncture application for functional constipation intervention conducted by Lee et al., the period of application was 4 weeks. In this study, to assess chemotherapy-related constipation among participants, 4 weeks was deemed sufficient. Thus, TAES was applied to the experimental group once a day for 4 consecutive weeks, six times per week, while participants were hospitalized for chemotherapy. Two weeks and 4 weeks after the chemotherapy, participants were assessed using the BSFS and CAS, respectively. At the end of the study, participants of both the groups were given a pen as thanks for their time and effort. Based on studies regarding TAES on constipation, four acupoints (Tianshu, Quchi, Zusani, and Shangjuxu) were stimulated, and these four points were effective in improving constipation [Table 1]. The TAES was applied in the following ways:

1. Participants were instructed to find a comfortable position for application of TAES. The skin condition of the abdomen was then assessed, and if it was normal, the skin surface was cleaned using cotton with alcohol.

2. The GI-I middle/low-frequency therapeutic apparatus (Beijing Simailaifu Medical Equipment Technology Co. Ltd., Beijing, China) was applied to TAES. Electrodes were placed at the acupoints of Tianshu, Zusani, Quchi, and Shangjuxu. Then, the

| Table 1: Location of acupoints for the transcutaneous acupoint electrical stimulation |
|----------------------------------|------------------------------------------|
| Acupoints | Location |
| Tianshu (ST25) | Levels with the umbilicus, 2 cun lateral to the anterior midline |
| Quchi (LI11) | In the depression of the radial end of the cubital crease when flex the elbow |
| Zusani (ST36) | Dubi acupoint is in the depression lateral to the patellar, ST36 3 cun below Dubi |
| Shangjuxu (ST37) | 3 cun below Zusani |
researcher chose “prescription 4” (aimed at GI disorders and constipation).

3. The researcher adjusted the frequency of electrical stimulation according to each patient’s tolerance. Patients experienced a slight twitch of the regional muscle upon electrical stimulation and a warm sensation upon application of the electrodes. Treatment could then commence.

4. TAES was provided daily for 30 min lasting for 4 weeks, six times per week.

   The optimal intensity of stimulation was regulated by individual maximum tolerance each day. After each session, participants made an appointment for the next session. Researchers answered questions of participants about this research in time. As the effect of the TAES was assumed to be different across patients, the patients were instructed to take less laxatives when they experienced improved constipation symptoms.

**Control group**

In the control group, the participants continued with the therapy they were already receiving prior to participation in the study: increased fiber intake, stimulant laxatives, or enemas. Compared with the TAES group, the control group was not instructed to decrease laxative use.

**Procedures**

The researchers completed 4-week courses provided by clinical specialists in the TCM department in a person. The performance of acupoint stimulation and their locations were confirmed by TCM experts. The interventions and data collection were performed by the investigators.

The purpose and details of the study were explained to those patients who agreed to participate, and written informed consent was obtained from all patients before randomization. Data were categorized before beginning the study (P1), 2 weeks after intervention (P2), and 4 weeks after intervention (P3). The following data were collected before the study: patient demographic information, disease characteristics, KPS scores, and scores on the BSFS and CAS. The assessment tools used in the study, the BSFS and CAS, were thoroughly explained to participants who then self-completed the scales. The researchers recorded disease-related information from participants’ medical records. The BSFS and CAS were administered to the experimental and control groups at the 2nd and 4th weeks; the experimental group received TAES, and the control group did not. The control group only received routine care, including health education, diet guidance, and abdominal massage (performed by patients themselves after being taught by nurses).

**Safety evaluation of transcutaneous acupoint electrical stimulation**

The safety evaluation included symptoms and average duration of skin allergies. After the intervention, none of the patients had any discomfort or reported any skin allergies. Thus, TAES is a safe treatment for relieving constipation. Both the groups used medication (laxatives or enema) as directed by their doctors if they suffered from constipation.

**Statistical analysis**

The primary endpoint was the CAS score change at baseline, 2 weeks, and 4 weeks. The secondary endpoints were the BSFS score changes at baseline, 2 weeks, and 4 weeks. Data were analyzed using SPSS software (version 22.0; IBM, Armonk, NY, USA). Demographic characteristics, disease-related characteristics, and major variable-related characteristics were analyzed through percentages, means, and standard deviations. The homogeneity of the experimental and control groups was analyzed through Chi-square test and Fisher’s exact test. Furthermore, differences in scores on the BSFS and CAS between the experimental and control groups were analyzed through repeated measures ANOVA. SPSS was used for data analysis, and GraphPad Prism (version 5.0; GraphPad Software, San Diego, CA, USA) was used for drawing the error bar.

**Ethical approval**

This study was approved by the Institutional Ethics Review Committee of of the Hunan Cancer Hospital, China (Approval No. 2017 year12). Before data collection, all participants were informed of the purpose and potential benefits/risks of the research. Participation was completely voluntary. Informed consent forms were signed after consent was obtained. The study was registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR1800018628).

**Results**

**Recruitment**

A total of 66 patients were randomly assigned to the intervention or control groups. Six patients withdrew during the study period and 90.9% completed the study. Four participants withdrew before the baseline because of lack of time and were excluded; one patient in the control group went on vacation and one patient in the intervention group reported being too weak to complete treatment. Ultimately, a total of 60 participants completed the study, with 30 patients per group. The data from those completing the study were analyzed (n = 60) [Figure 1].
Baseline characteristics

The demographic and disease-related characteristics of patients were collected, and the results of the homogeneity test are reported in Tables 2 and 3. According to the results on general and disease-related characteristics of participants, no statistically significant difference between the two groups was found, and therefore, homogeneity of the groups was confirmed.

Bristol Stool Form Scale

Scores for the BSFS were higher for the experimental group compared with the control group ($F = 9.23, P = 0.004$). A significant difference emerged on the measurement points (P1, P2, and P3) between the two groups ($F = 92.02, P < 0.001$). Scores for the experimental group were 2.93 ± 1.11 at P1, 4.13 ± 0.90 at P2, and 4.50 ± 0.86 at P3. The BSFS scores for the experimental group were higher than for the control group, and results reported that the application of TAES had a positive effect on stool form measurements [$F = 32.29, P < 0.001$; Table 3 and Figure 2].

Constipation Assessment Scale

The experimental group scores for the CAS were significantly lower compared with the control group ($F = 45.81, P < 0.001$), and a significant difference
emerged between the measurement points in the group ($F = 209.24$, $P < 0.001$). Scores on the CAS for the experimental group were 13.37 $\pm$ 2.14 at P1, 4.60 $\pm$ 3.16 at P2, and 3.73 $\pm$ 3.02 at P3. As the CAS scores for the experimental group were lower than those for the control group, the results indicated that the application of TAES had a positive influence on constipation measurements ($F = 23.59$, $P < 0.001$; Table 3 and Figure 3).

**Discussion**

This study assessed the effect of TAES on constipation among NSCLC patients who received chemotherapy. Participants who received TAES had increased BSFS scores and reduced CAS scores. TAES four acupoints (Tianshu, Quchi, Zusanli, and Shangjuxu) were demonstrated to be a useful intervention to alleviate constipation for NSCLC patients.

**Bristol Stool Form Scale**

The BSFS scores for the experimental group were significantly higher compared with the control group after intervention, which was similar to a previous study that reported an increase in BSFS scores after the application of TAES.$^{[30]}$ Using the acupoint Zusanli for intervention may be the reason. Another study proved that acupuncture and moxibustion (same TCM theory) at Tianshu (ST25), Zusanli (ST36), Shangjuxu (ST37), Daheng (SP15), Fujie (SP14), Qihai (RN6), and Guanyuan (RN4) to treat slow-transmission constipation was effective.$^{[31]}$ These results confirmed that all of these acupoints are effective in increasing BSFS scores, similar to the results derived from other complementary and alternative therapies.$^{[32,33]}$ However, a study that evaluated the effects of abdominal massage and meridian acupressure suggested no significant difference in BSFS scores between the experimental and control groups.$^{[34]}$ As the sample size was small and the intervention period was relatively short (only 2–4 weeks), the current study examined the effects of auricular acupressure on BSFS scores with a larger sample and for a longer period of time.

**Constipation Assessment Scale**

Significantly lower CAS scores in the experimental group resemble the results of a study (Park et al.) that reported alleviation of functional constipation among participants (identified with either qi (vital energy) deficiency or qi excess syndrome) through the application of moxibustion at four acupuncture points (Taiyi [ST23] and Daju [ST27], bilaterally) for the experimental group.$^{[35]}$ Although the same assessment tools were used in the current study, the score for the CAS was lower than in this study possibly because the sample used by Park et al. was small and the acupoints (ST23 and ST27, bilaterally) were

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**Table 3: Comparison of Bristol Stool Form Scale and Constipation Assessment Scale between the experimental and the control groups ($n=60$)**

| Variable | Group | Pretest | Posttest (after 2 weeks) | Posttest (after 4 weeks) | Source | $F$ | $P$ |
|----------|-------|---------|--------------------------|--------------------------|--------|-----|-----|
| BSFS     | Experimental group | 2.93±1.11 | 4.13±0.90 | 4.50±0.86 | G×T Group | 32.29 | <0.001** |
|          | Control group | 2.83±1.26 | 3.13±1.14 | 3.23±1.17 | Time | 92.02 | <0.001** |
| CAS      | Experimental group | 13.37±2.14 | 4.60±3.16 | 3.73±3.02 | G×T Group | 23.59 | <0.001** |
|          | Control group | 13.07±2.24 | 9.10±2.41 | 8.77±1.93 | Time | 209.24 | <0.001** |

**Figure 2:** Error bar of mean scores of the BSFS across three time points between the experimental and the control groups. BSFS: Bristol Stool Form Scale

**Figure 3:** Error bar of mean scores of the CAS across three time points between the experimental and the control groups. CAS: Constipation Assessment Scale
not useful for improving constipation symptoms. Another reason may be the intervention frequency. The study of Park et al. showed the effect of applying moxibustion three times per week for 4 weeks, whereas in this study, the intervention was applied six times per week for 4 weeks. Compared to the study of Park et al., there was a greater improvement in participant’s constipation symptoms as a result of TAES.

The current study, which applied TAES for constipation alleviation in NSCLC, was conducted for the first time in China. Although no TAES was provided to the control group, abdominal massage was offered, as has also been the case in previous studies. Therefore, further studies that add a sham group and study long-term effects are needed to confirm the effects of TAES.

No previous study globally has researched the effect of TAES on constipation-related symptoms among NSCLC patients undergoing chemotherapy. Thus, it is difficult to directly compare the results of this study with previous research. Nonetheless, the results from this study proved that TAES was effective in improving constipation-related symptoms and that TAES on certain acupoints could promote intestinal peristalsis, production, and resecretion of body fluid while improving GI function. [30]

The results of this study reported that intervention sessions had a positive effect on CIC. As the therapy was provided for 4 weeks, long-term effects emerged from the treatment. Therefore, TAES is an effective nonpharmacological intervention that should be included in the training syllabus of nurses and applied to clinical practice. As this therapy is a safe and easy-to-operate method of adjuvant treatment, it has great significance for clinical application.

Limitations

Some limitations to this research should be noted. First, as data were only collected twice during the 4-week intervention, memory bias may have increased, which could affect the results. In future studies, data collection should occur more frequently to avoid memory bias. Second, this study only included NSCLC patients receiving chemotherapy, and the results cannot be generalized to other cancer patients who receive other forms of treatment, such as surgery. Future studies should include different cancer diagnoses and treatments to increase generalizability. In addition, appropriate frequency and duration of TAES for each participant could be analyzed more precisely and more rigorous and validated sham TAES should be developed. Finally, the number of defeactions and laxatives used by each participant was not assessed at baseline.

Conclusions

The results of this research support the hypothesis that CIC in NSCLC patients could be relieved by TAES and that it is feasible to provide and implement TAES for chemotherapy patients. This study demonstrates the effectiveness of TAES for alleviating constipation, although additional studies are needed to determine the application of TAES to other treatments. Future studies should focus on acupoint compatibility for relieving CIC and improving the generalizability of the sample.

Financial support and sponsorship

This study was partially supported by the National Key Research and Development Program; the Key Technology of Palliative Care and Nursing for Cancer Patients (Grant No. 2017YFC1309200) and the TCM Research Project of Hunan Province (Grant No. 201994).

Conflicts of interest

The corresponding author, Prof. Yongyi Chen, is the editorial board member of the journal.

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