Cover Page of Research Project Application

For

Evaluation of the Efficacy of acupuncture in Chemotherapy-induced Peripheral Neuropathy

NCT03626220

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2017 Tainan Municipal An-Nan Hospital-China Medical University Research Project Application

A. Basic Information

Project Number： CMUH106-REC2-117

Project category	■Individual project	Principal Investigator of the Integrated General Project	
		Name of the Integrated General Project	
Project funding	■Medical research project ☐Biotechnology research project ☐Vendors/Manufacturers commissioned research projects ☐Others		
Project attributes	☐Biology division research project ■Non-biological division research project		
Project nature	☐Basic medical research ■Clinical research ☐Animal experiment research ☐ Biotechnology Research ☐ others		
Research experiences of applicants	■Within three years ☐More than three years ☐More than five years		
Principle investigator	Name：Chien-Chen Huang Affiliation：Department of Traditional Chinese Medicine, An Nan Hospital, China Medical University, Tainan, Taiwan, R.O.C. Position：Attending physician ID card Number：D221242291		
Co-investigators	Name：Tsung-Jung Ho Affiliation：Department of Chinese Medicine, Hualien Tzu Chi Hospital, No. 707, Sec. 3, Chung-Yang Road, Hualien, Taiwan 97002, R.O.C. Position：Vice Superintendent ID card Number：Q121025903		
	Name：Tsai-Wang Chang Affiliation：Department of Surgery, An Nan Hospital, China Medical University, Tainan, Taiwan, R.O.C. Position：Professor ID card Number：B100964109		
Title of project	Evaluation of the Efficacy of acupuncture in Chemotherapy-induced Peripheral Neuropathy		
Execution period	From August 1, 2017 to October 10,2020		
☐ Do not submit this project for external review ☐ Please avoid_____ doctor/professor review of this plan			
Project contact	Chien-Chen Huang	Phone Number	+886 912125682

B. Abstract

Please summarize the main points of this project within 500 words and customize the keywords according to the project's nature.

Keywords：acupuncture, chemotherapy-induced peripheral neuropathy

Peripheral neuropathy is currently the second most common side effect after chemotherapy, second only to the side effects of blood toxicity. A variety of chemotherapy drugs may induce peripheral neurotoxicity and be caused by the cumulative dose of chemotherapy drugs. Symptoms include sensory paresthesia, feeling dullness or numbness, glove-like feeling distributed in the palm. The currently most effective way is to interrupt the treatment or adjust the dose of chemotherapeutic drugs, but it is easy to make patients discontinue chemotherapy. The purpose of this study is to explore the impact of acupuncture on neurological symptoms and quality of life. Three kinds of questionnaires will be used:(1) Brief pain inventory- short form to assess the extent of pain and the impact of daily life. (2) FACT/GOG-NTX-13 (Version 4) assess changes in neurological symptoms; (3) WHOQOL-BREF to assess changes in patients' quality of life. The course of treatment was evaluated for nine weeks. Changes in neurological function and quality of life will be evaluated before treatment, the third week of treatment, the sixth week of treatment, till the ninth week. The aim of this study is to confirm that acupuncture can improve peripheral neuropathy after chemotherapy in order to enhance breast cancer patients' quality of life and provide a new opportunity for integrative therapy between Chinese and Western medicine.

C. Background and purpose of the research

Please describe in detail the background, purpose, and importance of this research plan, as well as domestic and international research on this plan and important references

(i) Background of the research

A variety of neurotoxic chemotherapeutic agents, including platinums (e.g. cisplatin, carboplatin, and oxaliplatin), taxanes (e.g. paclitaxel and docetaxel), and vinca alkaloids (e.g. vincristine and vinblastine), thalidomide and bortezomib, may induce peripheral neuropathy. Generally speaking, sensory nerve dysfunction is more common than motor involvement. It causes hands and feet to feel tingling, dullness or numbness symmetrically, a glove-like ("glove-and-stocking type") sensation distributed in palms and soles. Patient's touch, vibration, and proprioception senses may be impaired under clinical examinations[1].

CIPN relates to the cumulative doses of chemotherapeutic agents. Sometimes, when chemotherapy is stopped, neuropathy symptoms may continue or worsen, which is called a "costing phenomenon." Nerve damaging usually starts from the ends of the extremities; while individual doses were accumulated, it gradually extends to proximal joints or ganglions. CIPN is currently the second most common side, next to hematotoxicity. Within thirty days after chemotherapy, 68.1% of patients may develop CIPN, most of which can be relieved or improved, but there are still 30-83% symptoms persist over 6 months[1].

At present, the most effective way to treat CIPN is to stop the treatment protocol or adjust doses of chemotherapy; however, it affects the effect of chemotherapy in degrading tumor growth. Plenty of pharmacological or non-pharmacological treatments are still under investigation, such as antioxidant medication (e.g. Acetyl-L-carnitine, glutamine, vit B_{12}, fish oil, etc.), anxiolytics (e.g. venlafaxine), neuroprotective agents (e.g. infusion of calcium ions, magnesium ions), food supplements, acupuncture, light stimulation, etc. Acupuncture with the advantages of clinically effective, easy-practice and relatively safe, few studies revealed its effect on CIPN. However, there is still a lack of large clinical trials to evaluate its effectiveness[1].

(ii) Purpose of the research

To investigate the efficacy of acupuncture on peripheral neuropathy after chemotherapy administration in patients with breast cancer.

(iii) Importance of the research

Current studies revealed that acupuncture might be useful on CIPN; however, an insufficient number of participants or lack of control groups limit the quality of clinical studies. Therefore, the aim of our study to conduct a randomized controlled clinical trial to evaluate the efficacy of acupuncture on peripheral neuropathy caused by chemotherapy.

(iv) Domestic and international researches on this plan

In 2013, Giovanna Franconi et al. published a systematic review that screened the database of MEDLINE, Google Scholar, Cochrane Database, CINHAL, CNKI, Wanfang Med Online, ISI Proceedings. The screened year was set before 2012, and 3989 journal articles were screened. With excluding acupuncture irrelevant or duplicate articles, or researches unrelated to neuropathy and

chemotherapy, 98 papers left for quality evaluation, and 7 articles were selected finally which most relevant to the effect of acupuncture in treating CIPN. As the results of the two randomized controlled-trials selected in the seven articles, a prospective randomized controlled clinical trial conducted by Alimi et al. in 2003, auricular acupuncture for 2 months was significant improved in visual analog scale(VAS) compared with a controlled group(placebo acupuncture and seeds); another randomized controlled trial conducted by Tian et al. in 2011, warm acupuncture and moxibustion without knowing treatment duration, the quality of life and neurotoxic symptoms were improved compared with neurotropin [2].

Raimond et al conducted a phase II clinical trial in 2016, acupuncture-like transcutaneous nerve stimulation (ALTENS) was used in the experimental group, and the acupoints were patched on the seventh cervical vertebra in combination with Hegu, and the third Lumbar spine in combination with Tai-Chong. The protocol included 12 treatments, and 20 minutes remained in each treatment; all participants were followed up for 3 and 6 months from the end of treatments. Of 27 patients in ALTENS group, 24 completed the 3-month follow-up after treatment, and 23 completed the 6-month follow-up. Compared with the real acupuncture group, only 13 people were included. Although the results after acupuncture are listed, there were insufficient data to assess the differences between the two groups. Although studies have shown that ALTENS relieved symptoms of neurotoxicity using Modified total neuropathy score (mTNS), numbness score and Edmonton Symptom Assessment Scale (ESAS), there lacked a control group and randomized sampling design in this study[3].

Heather Greenlee et al. conducted a pilot study comparing electro-acupuncture(EA) and sham electro-acupuncture(EA) to prevent taxane-induced peripheral neuropathy. Yanglingquan, Zusanli, Shousanli and Hegu were the main acupoints in the EA group, in addition of acupoints in upper limbs, such as Huatuo Jiaji(C5, C7) and Bafeng acupoints, and Huatuo Jiaji(L3, L5) and Baxie in lower limbs. Park sham collapsible acupuncture was used to touch the acupoints without penetration in the sham electro-acupuncture group. 12 weeks of treatment were designed, and 30 minutes for each treatment. The neurological patient-reported outcomes included Brief Pain Inventory-Short Form (BPI-SF), Functional Assessment of Cancer Therapy-Taxane (FACT -TAX), FACT-NTX, and Neuropathic Pain Scale (NPS) were assessed at week 6, week 12, and week 16. Qualified participants, who completed at least 3 weeks of treatment, pre-treatment, and at least one follow-up questionnaire in each group, were comparable. However, there were no significant differences between EA group and sham EA group in neurological assessments. Further studies should be conducted to evaluate the effectiveness of acupuncture in the prevention of CIPN[4].

(v) Important references

1. Susanna B.Park, David Golstein, et al; Chemotherapy-Induced Peripheral Neurotoxicity: A critical Analysis. *CA CANCER J CLIN*. 2013;63:419-437.
2. Giovanna Franconi, Luigi Manni, et al; A Systematic Review of Experimental and Clinical Acupuncture in Chemotherapy- Induced Peripheral Neuropathy. *Evidence-Based Complementary and Alternative Medicine*.2013:p1-7.
3. Raimond Wong, Pierre Major, et al: Phase 2 Study of Acupuncture-Like Transcutaneous Nerve

Stimulation for Chemotherapy-Induced Peripheral Neuropathy. *Integrative Cancer Therapies*. 2016; 15(2):153-164.

4. Heather Greenlee, Katherine D. Crew, et al: Randomized Sham-Controlled Pilot Trial of Weekly Electro-acupuncture for the prevention of Taxane-induced Peripheral Neuropathy in Women with Early Stage Breast Cancer. *Breast Cancer Res Treat*. 2016;156:453-464.

D. Research methodology and procedures

1. Please elaborate on the research methodology and reasons used in this project.
2. Expected difficulties and solutions
3. Cooperative use of essential instruments.
4. For projects that last more than one year, please list them by year.

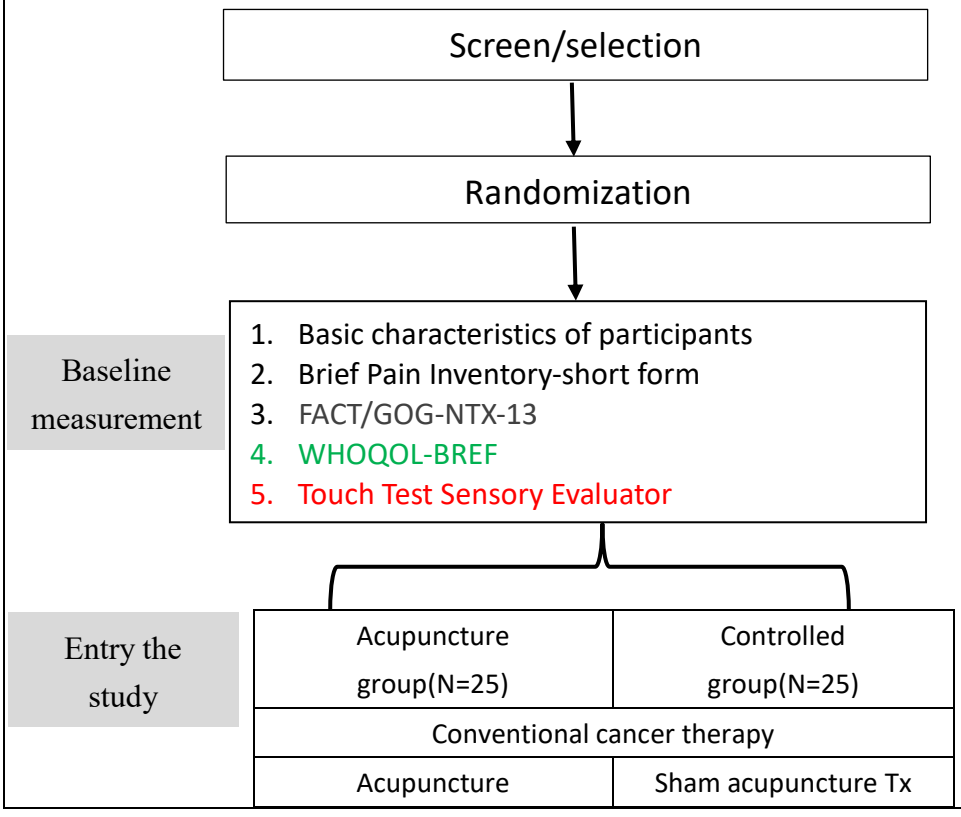
(i) Research methodology and reasons

This randomized controlled clinical trial explores the efficacy of combined acupuncture and drug treatment (conventional cancer therapy) in women with breast cancer after chemotherapy causes peripheral neuropathy. The study adopted convenience sampling and randomized allocation, all the participants were screened from the patients with breast cancer who visited the Department of Traditional Chinese Medicine at Tainan Municipal An-Nan Hospital-China Medical University, Tainan. Taiwan.

The inclusion criteria will be: female more than 20 years of age; breast cancer with early-stage at I-III; had completed chemotherapy; the neurotoxic chemotherapeutic agents included taxanes, platinums, or others; less than grade three in the Eastern Cooperative Oncology Group (ECOG) status; higher than grade one in National Cancer Institute-common terminology criteria for adverse events(NCI-CTCAE) scale.

The exclusion criteria will be: having less than three months in mean survival time, history of diabetic neuropathy before chemotherapy administration, history of other preexisting peripheral neuropathy, other inflammatory or metabolic arthritis, severe blood coagulation diseases or with latent bleeding tendency, unstable cardiovascular diseases, or other preexisting muscle-skeletal diseases.

Figure 1 showed the flow chart of the research:



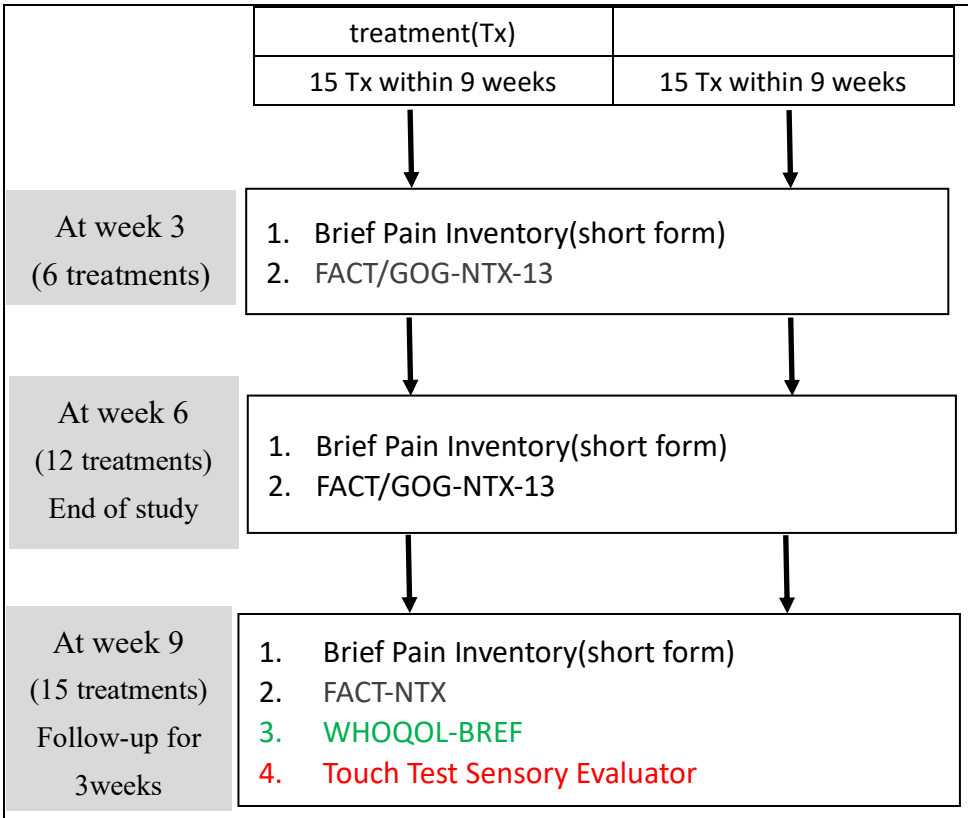


Figure 1. The flow chart of the study

The evaluation tools used in the research are:

(1) Brief Pain Inventory-short form: To assess the location of pain and the level of pain. Items are scored from 0 to 10 (0= no pain; 10= pain as bad as you can imagine) to evaluate the degree of pain and the impact of pain on daily life.

(2) FACT/GOG-NTX-13: To evaluate the changes in peripheral neuropathy such as sensory, motor, touch, cold and heat sensations, and the impact of pain on daily life. Items are scored from 0–4 (0 = not at all; 4 = very much) and summed.

(3) WHOQOL-BREF (Taiwan version): To evaluate the degree of improvement in the quality of life after receiving acupuncture treatment. Items are scored from 1–5 (1 =being very dissatisfied, 2 =dissatisfied, 3 =No comments, 4 =satisfaction, 5 =very satisfied).

(4) Touch Test Sensory Evaluator: Use 20 von Frey monofilaments to test the degree of the tactile sensation of the patient's fingertips, tips of the toe, palms, and planters.

The treatment protocol will be designed as:

(1) The acupuncture group: Acupuncture treatment will be performed for 9 weeks. The frequency of acupuncture will be twice a week for the first six weeks, and once a week for the following three weeks. 30 minutes needling at each treatment. Acupuncture points include Baihui(GV20), Qihai(CV6), Quchi(LI11), Hegu(LI4), Neiguan(P6), or Shenmen(HT7) for upper limbs. For plantar numbness, choose two acupoints to use in turn; use Weizhong(BL40), Sanyinjiao(SP6), or Zusanli(ST36) for lower limbs. If severe numbness occurred, Taixi(KI3) or Yongquan(K1) should be added for feet numbness. “De qi” sensation, such as soreness, numbness, pain, etc. will be achieved at each acupoints .

(2) The controlled group: Acupuncture with minimal needling 0.5 *cun* (estimated 1cm with deviation depends on the body size of each participant) away from the acupoints, which only superficially penetrated the skin without the feeling of "De Qi" sensation.

The conventional cancer treatment for CIPN was the same in the two groups.

Within nine weeks of treatments, questionnaires were assessed before treatment, at week three, week six, and week nine to follow-up the changes of peripheral neuropathy on each participant.

Explore the neuroprotective mechanism of acupuncture: 15 cc of blood samples will be drawn before and after 15 sessions of treatments from participants in both groups. The blood samples will be analyzed by enzyme-linked immunosorbent assay (ELISA) for tumor necrosis factor-alfa and interleukin- 6, interleukin-10 and brain-derived nuerotrophic factor to evaluate the differences in the inflammation state of the peripheral nervous system within and between groups.

Statistical analysis:

This is a two-group, parallel controlled clinical trial; the null hypothesis will be no significant difference in BPI-SF between the two groups. The estimated standard deviation was 2, the power was set to 94%, a two-tail test, α=0.05, and the estimated number of patients was at least 25 in each group.

A two-sample t-test will be used to compare the difference between the treatment group and the controlled group.

A Paired-t-test will be used to compare the changes in the assessment scale at week 3, week 6 and week 12.

One way ANOVA: Analyze the relationship between the demographic data of subjects, breast cancer grade and other category variables and the evaluation scale.

(ii) Expected difficulties and solutions

The treatment group often withdrew from the trial due to frequently acupuncture or bleeding caused by acupuncture. The solution is to specify the possible side effects of acupuncture, such as bleeding or bruising, in the informed consent form.

The control group may not be able to continue treatment due to low efficacy. The way of solution is to strive for subject allowances.

E. The expected work items and specific results

1. Please list the work items expected to be completed within the implementation period.
2. Expected contributions to academic research, national development and other applications.
3. Expected training for participating staff members.
4. For projects that last more than one year, please list them by year.

(i) Work items expected to be completed within the implementation period

1. To submit the protocol to the Research Ethics Committee of the hospital for ethical review.
2. To establish patients' basic characteristic datasheets.
3. To obtain authorization and preparation of assessment scales
4. To update related articles in journals or books about the study
5. To pre-test and adjust study procedures.
6. To screen eligible participants and complete the assessments
7. documentation of study data.
8. statistical analysis.
9. Prepare an interim report
10. Prepare results reports
11. Send an application for the research funding.

(ii) Expected contributions

Until now, most studies focused on the effect of acupuncture or traditional Chinese formulas in the treatment of CIPN. The aim of this study is to investigate the effect of acupuncture with conventional cancer therapy in the treatment of CIPN, in order to prove the effect of intervention with traditional Chinese medicine in treating cancer treatment-related symptoms.

(iii) Expected training for participating staff members

The staff participating in the research will understand the research ethics, the process of experimental design, the importance of the informed consent form, and the authorization and preparation of evaluation tools. Through data collection and analysis, the staff can learn how to use statistical software, data analysis, and write credible professional medical articles.