The efficacy and safety of acupuncture for alleviating chemotherapy-induced peripheral neuropathy in colorectal cancer patients: study protocol for a pilot single-blinded, randomized sham-controlled trial

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Study protocol

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Abstract

Background: Colorectal cancer is the most common cancer in Hong Kong. Oxaliplatin based chemotherapy is a major first-line conventional therapy for advanced and metastatic colorectal cancer. However, oxaliplatin causes chemotherapy induced peripheral neuropathy (CIPN). Acupuncture has been recognized as one of the effective intervention for preventing CIPN. This study aims to examine the efficacy and safety of acupuncture for preventing CIPN in colorectal cancer patients in Hong Kong. Methods/Design: This is a pilot single-blinded, randomized, sham- controlled trial. Eighty-four eligible patients, who are Hong Kong Chinese aged ≥18 years and are diagnosed as colorectal cancer undergoing oxaliplatin based chemotherapy, will be randomized in a ratio of 1:1 to acupuncture group and sham-controlled group. During 12-weektreatment period, patients in acupuncture group will undergo acupuncture once a week from the first cycle of chemotherapy, patients in control group will receive sham-acupuncture, and the patients in both groupswill be followed up for twelve weeks. The primary outcome measure is the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOC-Ntx) questionnaire. The secondary outcome measures include numerical rating scale (NRS), vibration and light touch sense test, quality of life questionnaire-C30 of European Organization for Research and Treatment of Cancer (EQRTC) (EORTC QLQ-C30) and Constitution of Chinese Medicine Questionnaire (CCMQ). Discussion: The study will compare acupuncture with sham acupuncture and will obtain evidence for utilizing acupuncture for chemotherapy induced peripheral neuropathy.

Background

Colorectal cancer is the most common cancer in Hong Kong. In 2016, there were 5437 new cases and 2089 patients died due to colorectal cancer. Its crude death rate was 28.5.[1] in Hong Kong. Current conventional therapies for of colorectal cancer are surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, etc. Surgery is the most common treatment for all stages of colorectal cancer and patients with advanced stage usually should be given chemotherapy or radiotherapy to kill any cancer cells that are left. Oxaliplatin based chemotherapy, regimens such as FOLFOX ±bevacizumab, CapeOX ± bevacizumab or FOLFOX ± panitumumab (KRAS wild type gene only), is one of the major treatment for advanced or metastatic colorectal cancer at first-line therapy[2]. However, 90% of patients with oxaliplatin developed acute chemotherapy induced peripheral neuropathy (CIPN)[3] and occurred in 68.3% patients from 2.5 ± 1.1 (mean ± standard deviation) chemotherapy cycles[4]. Its symptoms include parenthesis, dysesthesia of the hands and feet and perioral area induced by cold stimuli[5]. About 30-50% of patients developed chronic CIPN after repetition of chemotherapy cycles[3] and its symptoms were paresthesia, numbness, sensory ataxia, functional deficits and pain. The mechanism of CIPN is complicated. Cytokine and chemokine binding are one of its possibility. Chemotherapeutic agents enhance cytokine release e.g. TNF-α, IL-1βand chemokine bind to the receptors located on neurons and glial cells and increase pain6.Electro-acupuncture can treat CIPN and its analgesic mechanism was related to decrease the proinflammatory cytokine TNF-α, IL-1α, IL-1βlevel7. CIPN had no vegetative disturbances but had

coasting effect, which mean that the symptoms may continue to develop and progress for several months post-therapy, and its maximum duration in the literature was 8 years[5].

In Traditional Chinese Medicine's theory, CIPN is similar to "Xue Bi"(□□), which has pain and numbness in the extremities[8]. Herbal medicine and acupuncture is a common treatment for "Xue Bi". Systematic reviews of the CIPN found that the effectiveness of current treatments (included natural products and complementary therapies) were still unknown and only vitamin E may help prevent CIPN[9,10]. The current studies of acupuncture for CIPN was varied in different cancer and anti-cancer drugs such as taxanes for breast cancer[11], bortezomib and thalidomide for multiple myeloma[12], and a mix of neurotoxic anticancer drugs[13]. However, studies of acupuncture for oxaliplatin induced peripheral neuropathy are rare and no randomized controlled trial was done[14]. Therefore, we design this single-blinded, randomized controlled clinical trial to explore the efficacy and safety of acupuncture on prevention of CIPN.

Objective

The aim of the study is to assess the efficacy and safety of eletro-acupuncture compared to sham acupuncture on alleviating chemotherapy-induced peripheral neuropathy (CINP) in colorectal cancer patients.

Methods/design

Study design

This is a single-blinded, randomized, sham-controlled trial on electro-acupuncture for alleviating symptoms of chemotherapy induced peripheral neuropathy in patients with colorectal cancer. This study is conducted at Yan Chai Hospital cum Hong Kong Baptist University Chinese Medicine Clinic sum Training and Research Centre (Ha Kwai Chung). Subjects will be recruited through either of the following sources: (1) advertisement on newspaper; or direct recruitment from the Princess Margaret Hospital oncology outpatient department and Yan Chai Hospital cum Hong Kong Baptist University Chinese Medicine Clinic cum Training and Research Centre (Ha Kwai Chung). Patient who (1) are suffering from colorectal cancer, (2) age over 18, (3) are planning to receive oxaliplatin-based chemotherapy and, (4) do not have any pre-existing peripheral neuropathy, will be included in the study. An informed consent will be taken from eligible patients. A total of 84 candidates will be recruited in this study. They will be assigned randomly into either the electro-acupuncture or sham-control group. Both groups will be given a total of 12 sessions of interventions, with 1 session per week. They will be followed up to 12 weeks upon completion of intervention. The Functional Assessment of Cancer Therapy/Gynecology Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire will be used as the primary outcome measured. The questionnaire will be done before start of the study as a baseline score. The score will be obtained on

weekly basis during both the intervention and follow-up period, up to 24 weeks.(Fig. 1) This study protocol has been approved by Hong Kong Baptist University Ethics Committee on the Use of Human Subjects for Teaching and Research (Approval no. HASC/17-18/C05) and Hospital Authority Kowloon West Custer Research Ethics Committee (Approval no. KW/FR-18-041(121-01)) and registered in Clinicaltrials.gov (NTC03582423). The checklist for items in STRICTA 2010 is given in **Table 1.**

Participants

Setting

The study is conducted in the Yan Chai Hospital cum Hong Kong Baptist University Chinese Medicine Clinic cum Training and Research Centre (Ha Kwai Chung).

Inclusion criteria

Patients will be eligible for the study if they:

- age ≥18 years old;
- are newly diagnosed with stage □to □colorectal cancer;
- plan to receive 8 cycles of adjuvant oxaliplatin-based chemotherapy;
- have not received any acupuncture in the previous 3 months; and have a life expectancy ≥ six months

Exclusion criteria

Patients will be excluded from the study if they:

- are not able to comprehend and communicate;
- are failed to cooperate with the researcher;
- are not able to read Chinese;
- have prior peripheral neuropathy caused by other diseases including diabetes, stroke, cardiovascular diseases such as arrhythmia, heart failure, myocardial infarction, and patients with cardiac pacemakers;
- have a bleeding tendency;
- are pregnant or giving breast-feeding
- have impaired hepatic or renal function;

are using any pharmaceutical agents e.g. vitamin B6 and vitamin E, or herbal medication for CIPN treatment. All the above medication prescribed by physicians or Chinese medicine practitioners during the study will be recorded. Investigators will determine whether they need to be withdrawn from the study. Candidates will be considered as drop-out from the study if they:

- withdraw his/her informed consent;
- stop taking the randomized treatment for any reason;
- lost to follow-up;
- develop serious adverse event (SAE) or other safety/ efficacy issues in which suspension will be considered beneficial as suggested by investigators;
- becomes pregnant

The date and reason for withdrawal should be noted in the case report form (CRF). All subjects who withdraw from the study should, if all possible, be seen for a final evaluation (Termination Visit). Prematurely discontinued subjects will not be replaced.

Interventions

Eletro-acupuncture treatment

Acupuncture intervention will be conducted for one session per week over 12 consecutive weeks. The most frequently used acupuncture points in CIPN are ba feng (EX-LE10), ba xie (EX-UE9), tai chung (LV3), he gu (LI4)[15]. Among them, the traditional effects of the points in hands and feet are regulating Qi and blood circulation and treating localized problems. With the clinical experience of our principal investigator and co-investigators, eight acupoints are chosen: he gu (LI4), nei guan (PC6), qu chi (LI12), ba xie (EX-UE9), zu san li (ST36), san yin jiao (SP6), tai chung (LV3) and ba feng (EX-LE10). The use of ba xie (EX-UE9) and ba feng (EX-LE10) will be optional if skin lesions of hands and feet occurs due to Capecitabine (Xeloda). The details of acupoints and their functions are listed in **Table 2**. The acupuncture treatment will be conducted by a registered Chinese medicine practitioner with more than 5 years of Chinese medicine college education plus at least 5 years of clinical experience.Disposable acupuncture needles (verum acupuncture needles Hwato 0.25×25mm matching the Streiterger sham needles) will be inserted at a depth of 10-25mm into the points. We will deliver electrical stimulation with continuous waves at 2 Hz, at an intensity of each patient's minimum sensation of stimulation through the electrical acupuncture stimulation instrument (KWD808I multi- purpose health device, Ying Di, Chang Zhou, China) to the points. The needles will be retained in position for 25 minutes.

Sham acupuncture

For subjects assigned to the control group, Streitberger's non-invasive acupuncture needles (Gauge 8 × 1.2"/ 0.30 × 30mm) will be applied to serve as a sham control at the same acupoints with the same stimulation modality, except that the needles are only adhered to the skin by a small plastic ring instead of being inserted[16,17]and the stimulation will be a "pseduostimulation", which will be given by connecting the needle to incorrect output socket of the electrical acupuncture stimulation instrument. The credibility and validity of this system has been well demonstrated[18,19].

Outcome measures

The primary outcome is the validated Functional Assessment of Cancer Therapy/Gynecology Oncology Group/Neurotoxicity (FACT/GOC-Ntx) questionnaire[20, 21]. The questionnaire includes 11 questions covering sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy. It results in a cumulative score ranging from 0 to 44, with the higher scores reflecting worse neuropathy symptoms. The secondary outcomes include (1) numerical rating scale (NRS) of numbness/pain score in hands and feet[21], which patients will be asked to rate their average neuropathy symptoms within one week, on an 0 to 10 scale (0 = no symptoms; 10 = worst possible symptoms), those <4 of 10 NRS will be considered as mild CIPN while ≥4 of 10 NRS will be considered as moderate to severe CIPN[22]; (2) the validated European Organization for Research and Treatment of Cancer (EORCTC) quality of life questionnaire QLQ-C30[23], which is a 30-items questionnaire assessing five functional scales (physical, role, cognitive, emotional and social), three symptoms scales (fatigue, pain, nausea and vomiting), and other symptoms and problem in cancer patients (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties); (3) the validated Constitution of Chinese Medicine Questionnaire (CCMQ)[24,25], which has 60 items measuring the 9 body constitution types: gentleness, Qi-deficiency, Yang-deficiency, Yin-deficiency, phlegm-wetness, wetness- heat, blood-stasis, Qi-depression, and special diathesis; (4) vibration sense test, which It is assessed using the graduated Rydel-Seiffer tuning fork (U.S. Neurologicals, Poulsbo, WA), with printed directions for use and its normative data[26]. Readings will be averaged and recorded as the vibration value. (5) light touch test, which is assessed with standard 10g monofilaments, contained within the Neuropen (Owen Mumford, Woodstock, UK). During testing, the fiber will be applied perpendicular to the plantar surface of the great toe and the palmar surface of the index finger until the fiber begins to bend and will be held in place for 1 second and removed. This will be repeated 3 times and the patient will be asked to report the ability to feel the fiber when it is applied[26]. The use of the above assessment questionnaires (FACT/GOC-Ntx, QLQ-C30 and CCMQ) will be required authorization from the authors. Besides at baseline (0 week), FACT/GOC-Ntx 11 items subscale, NRS, vibration sense test and light touch test will be assessed every week, EORTC QLQ-C30 will be assessed every 3 weeks, CCMQ will be assessed at the end of treatment (12^{th} week). The post-trial access by phone or interview will be performed at 15^{th}, 18^{th}, 21^{st} and 24^{th} week. The schedule of evaluations is presented in **Table 3**. Adverse events will be noted throughout the study, based on the participants reports and routine laboratory tests (complete blood counts, renal and liver functions) before

every chemo-cycle. Subjects will undergo routine laboratory tests before every chemo-cycle for complete blood counts, renal and liver functions in hospitals where they received chemotherapy. Lab reports will be collected and thus any adverse events will be reported and noticed. All clinical adverse events will be recorded according to terms of intensity (mild, moderate or severe), duration, outcome and relationship to the study.

Randomization assignment

All subjects will be assigned to either the intervention or sham-control group randomly. Subjects in intervention group will receive electro-acupuncture treatment, whereas the subjects in the sham-control group will receive the sham treatment. A simple, non-sequential random numbers in a block of four will be generated by a computer program prior to randomization. These numbers will be kept by the principal investigator (PI). A sealed envelope containing the randomization number which corresponds to the group allocation will be provided to the acupuncturist by the PI. Both the clinical assessor and subjects are thus blinded to the group allocation. If there are medical concerns leading to an inevitable review of treatment assignment, the PI will be the responsible person for approval. The date, time and reason for treatment assignment disclosure should be noted in the CRF. Upon disclosure of treatment assignment, the concerned subject must be withdrawn from the study. The data of the concerned subject will be included in the analysis up to the date and time of treatment assignment disclosure.

Sample size calculation

The sample size calculation is based on the change of primary outcome. In this study, the difference in FACT/GOC-Ntx score between the intervention group and the sham-control group accounts for the calculation. As shown in a recent systematic review[14], there was only one study showing that acupuncture has significantly reduced the FACT GOC-Ntx score (MD = 5.40, SD = 3.91, 95% CI = 0.54-10.26)[27]. In this study, we assume the effect size between eletro-acupuncture and sham acupuncture is 0.3. A minimum sample size of 62 should therefore be provided in order to achieve a significance level of $\alpha = 0.05$ with power $(1-\beta)$ of 80%, [number of measurements is 3 and correlation among repeat measures is 0.5]with calculation by Gpower 3.1 (F tests, ANOVA, repeated measures, between factors). After taking 25% of dropout rate into consideration, the number of subjects for this study should raise to 84.

Data processing and analysis

All The efficacy and safety analyses will be based on intention-to-treat (ITT) principle. Any missing values will be imputed by the last-observation-carried -forward method. Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 will be used for the statistical analysis. The statistical

significance is defined as two-sided *P* value of < 0.05. Baseline characteristics will be reported as mean and standard deviation (SD). The differences in both the normally distributed and non-normally distributed variables between the intervention and the sham-control groups will be assessed through Student's t test and Mann-Whitney U test respectively. The chi-sqaured test or Fisher's exact test will be used for calculating the categorical variables instead. Analysis of covariance (ANCOVA) will be used for the comparisons between the two groups every week, with treatment group as a factor in the model and baseline as the covariate. The difference between the baseline and endpoint score will be tested by using repeated measure analysis of variance (ANOVA). Paired t test and Wilcoxon signed-rank test will be used for analyzing the within-group data which are normally distributed and non-normally distributed respectively. Any deviation from this original statistical plan will be described and justified in the final report. All study files will be archived for 3 years upon completion of the final report. Only the principal investigator, co-investigators, site supervisor, KWC REC and HA Chinese medicine department are the authorized parties to access to these personal data.

Discussion

This single-blinded, randomized controlled clinical trial aims to evaluate the efficacy and safety of acupuncture on chemotherapy induced peripheral neuropathy (CIPN) of colorectal cancer patients in Hong Kong. It will be the first of such study on Hong Kong population and will obtain evidence for utilizing acupuncture in CIPN treatment especially for patients who are receiving chemotherapy. The outcome measures will include the quality of life and body constitution of Chinese medicine which will provide data to us on analysis of the treatment's potential benefit on the above items.

So far there is no such kind of study in Hong Kong and this will provide evidence for large-scaled research such as combined therapy on CIPN with Chinese herbal medicine intervention. Further research on the side effects of chemotherapy or integrated medicine can also be developed specifically targeting on different types of cancer patients.

In this clinical trial, the selection of acupoints is standardized and utilized to every subject. It may help easier utilization on the treatment over different individuals but the limitation is that the selection of acupoints is not based on Syndromes differentiation which is the main concern in traditional Chinese acupuncture. Another limitation is the small sample size as the trial was proposed to be a pilot study for later large-scaled clinical trial.

In conclusion, in this pilot study, a single-blinded, randomized controlled clinical trial will be conducted to evaluate the effectiveness, efficacy and safety of acupuncture on CIPN in Hong Kong. This study will

obtain the solid evidence for CMPs to utilize acupuncture for CIPN and will also provide a platform to offer research training opportunities for junior CMPs.

Trial status

This study protocol version number is 4 which dated on 26 Feb 2019. The participants are currently being recruited for the present study since October 2018. Thirty-three patients are under treatment and recruitment will be completed on December 2019.

Abbreviations

Analysis of Covariance, ANCOVA; Analysis of Variance, ANOVA; chemotherapy induced peripheral neuropathy, CIPN; Acupuncture; Chinese Medicine practitioners, CMPs; Intention-to-treat, ITT.

Declarations

Ethics approval and consent to participate

This study protocol has been approved by Hong Kong Baptist University Ethics Committee on the Use of Human Subjects for Teaching and Research (Approval no. HASC/17-18/C05) and Hospital Authority Kowloon West Custer Research Ethics Committee (Approval no. KW/FR-18-041(121-01)). Consent is obtained from every participant.

Consent for publication

Written informed consent was obtained from the patient(s) for publication of this manuscript and accompanying images.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No competing financial interests exist.

Funding

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Authors' contribution

Kaiyin Chan drafted the manuscript and Linda Zhong revised the manuscript. Kaiyin Chan, Linda Zhong, Zhao-Xiang Bian, Bacon Ng designed and supervised the study. Louisa Lui was responsible for the monitoring the safety of the patients and prescribing the laboratory tests. Kaling Yu, Kwongwai Lau, Manchi Lai, Waiwai Lau will do the data analysis and conduct the study. All authors have read and approved the final manuscript.

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chemotherapy-induced peripheral neuropathy. Evid. Based. Complement. Alternat. Med. 2013, 928129 (2013).

Table And Figure Legends

Figure 1. Participant flow diagram

Table 1. Checklist for items in STRICTA 2010

Table 2. acupoints of eletro-acupuncture and their location

Table 3. schedule for outcome measurement

Figures

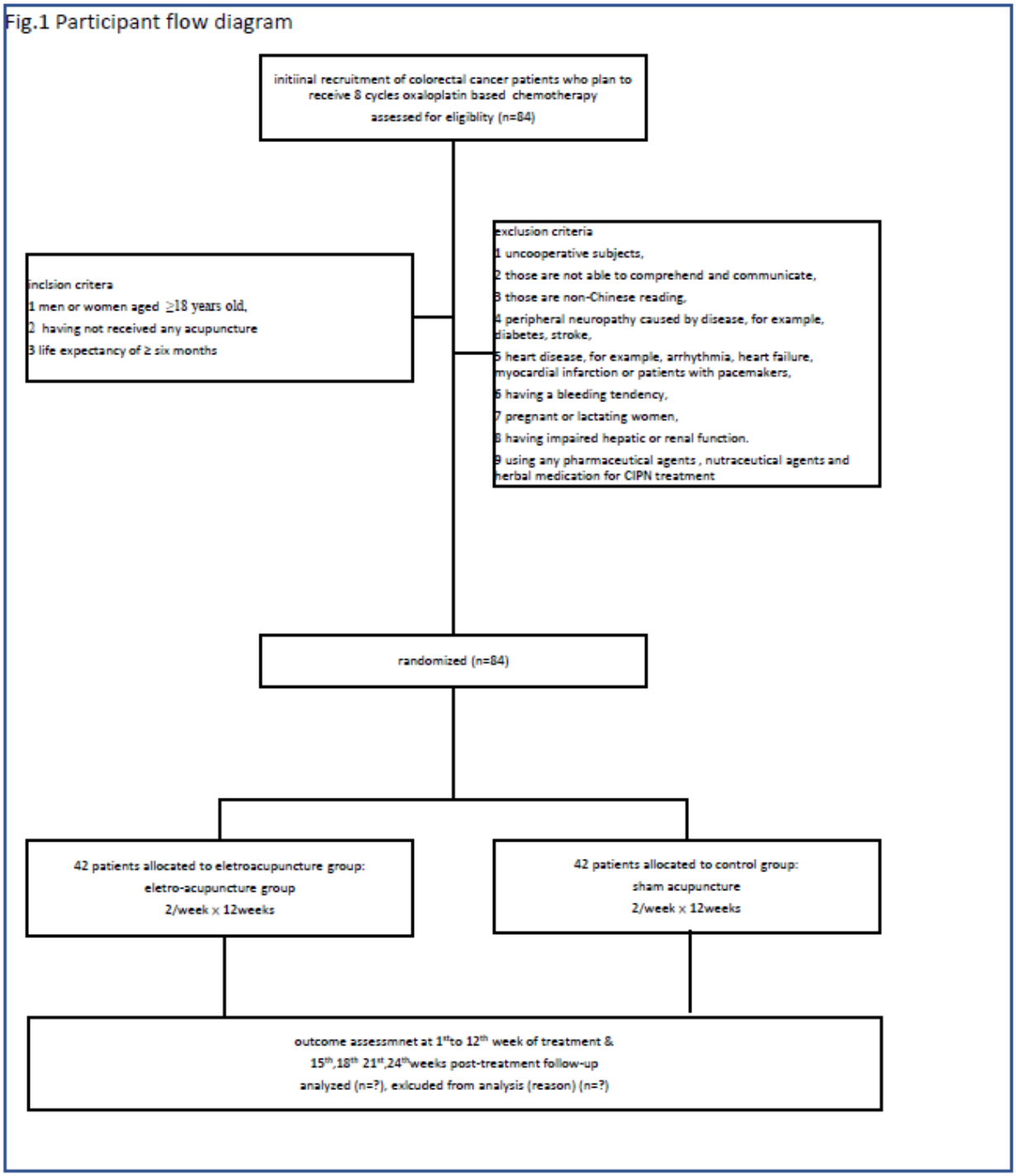

Figure 1

Participant flow diagram

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