BMJ Open  Effect of Fu’s subcutaneous needling for cancer pain management: protocol for a pragmatic randomised controlled trial

Danghan Xu,1 Zhanbo Yu,2 Ximin Cai,2 Jietao Lin,3 Tengjiao Lin,4 Jian Sun,5 Zhaoxi Liu,2 Yang Cao 6 Yihan He 6

ABSTRACT

Introduction  Pain is a common symptom in patients with cancer, and pain management is crucial for these patients. Fu’s subcutaneous needling (FSN) is a modern acupuncture therapy based on basic medicine commonly used in patients with pain. However, evidence of its effectiveness in treating cancer pain has not been systematically proven. Therefore, this pragmatic randomised controlled trial aims to evaluate the effectiveness and safety of FSN for cancer pain management.

Methods and analysis  Overall, 120 eligible patients will be recruited and randomly assigned into two groups using block randomisation. Both groups will be administered analgesic drugs according to the National Comprehensive Cancer Network guidelines. The treatment group will receive FSN therapy one time a day for 6 days. Additionally, we will assess analgesic consumption as the primary outcome and the Numerical Rating Scale, outbreak pain, symptom assessment and adverse events as secondary outcomes to evaluate the effect and safety of FSN in treating cancer pain. The incidence of adverse events will be monitored to assess the safety of FSN.

Ethics and dissemination  Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval No. K(2021)096). The results will be published in a peer-reviewed journal, and trial participants will be informed via email and/or phone calls.

Trial registration number  ChiCTR2200056348.

INTRODUCTION

With the incidence of cancer increasing, cancer pain has attracted significant attention from clinical practice. It was estimated that there would be more than 1.9 million new patients with cancer in 2022 in the USA,¹ and more than 40% of cancer survivors experience cancer pain.² These patients also experience cancer pain-related symptoms, such as aches, fatigue, anxiety and insomnia,³ because cancer pain is a comprehensive symptom. Opioids or non-opioid drugs are provided by the physician to patients with cancer primarily depending on the intensity of the pain.⁴ However, opioid-related adverse effects can affect the usage of opioids for cancer pain.³

Medication treatment regimens can be insufficient to treat symptoms related to cancer pain. Therefore, integrative oncology, which includes acupuncture and its related therapies, has been proposed to address these problems.⁶–⁸ Fu’s subcutaneous needling (FSN) therapy, which is a modern acupuncture technique,⁹ is used in cancer pain management. FSN therapy is an innovative method of acupuncture that was initiated by Dr Zhonghua Fu in 1996. It is based on traditional academic acupuncture practice combined with modern medical treatment. This therapy is based on concepts of pathologically tight muscles and beneficial reperfusion activity and emphasises the myofascial trigger point.¹⁰ It uses a special disposable needle to sweep the superficial subcutaneous fascia around the localised pain, combined with reperfusion activities to improve local circulation and eliminate ischaemia. Recently, FSN therapy has become popular in China for pain treatment,¹¹–¹³ and cancer pain management. A case series report indicated that FSN therapy produces analgesic effects.¹⁴ Furthermore, Liu et al showed that FSN therapy could improve the quality of life of patients with cancer experiencing pain.¹⁵ Another trial found that adjuvant FSN therapy administered to treat moderate pain in patients

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This real-world study may complement the clinical indications for Fu’s subcutaneous needling therapy.
⇒ This study suggests a new management method for cancer pain and may have implications for addressing opioid abuse.
⇒ The hospital included in this study is not internationally representative; therefore, the findings may not represent practice in other hospitals or countries.
⇒ Our conclusions may be limited due to a single centre design without blinding.
⇒ Other ‘real-world’ factors may influence the data and its interpretation in this pragmatic study.

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For numbered affiliations see end of article.

Correspondence to Dr Yihan He; yihanhe@gzucm.edu.cn
with advanced cancer can decrease the required dosage of analgesics.\(^\text{16}\)

However, evidence-based clinical research on cancer pain with FSN therapy is currently limited,\(^\text{17}\) with certain flaws in research design and a high risk of bias, such as inappropriate control, incorrect randomisation allocation or improper sample size calculation. The above problems must be addressed to promote FSN’s clinical application in treating cancer pain. Therefore, we aim to perform a pragmatic trial with a rigorous design to evaluate the efficacy and safety of FSN therapy in comprehensive cancer pain management.

METHODS AND ANALYSIS

Study design

This study will be conducted at the First Affiliated Hospital of Guangzhou University of Chinese Medicine from March 2022 to December 2024. This study will promote the clinical practice of FSN in treating cancer pain.

This study will be performed according to the Declaration of Helsinki. The study protocol will be reported based on the Standard Protocol Items: Recommendations for Interventional Trials guidelines. The recruiters will be responsible for screening patients for eligibility and assisting them in filling out voluntary informed consent forms in the inpatient department. After screening for eligibility, 120 patients will be randomly assigned to the treatment or control groups using block randomisation. Both groups will receive basic analgesics according to the National Comprehensive Cancer Network (NCCN) guidelines. The treatment group will also receive FSN therapy one time a day for 6 days. Patients will be assessed for analgesic consumption, the Numerical Rating Scale (NRS), outbreak pain and the Edmonton Symptom Assessment System (ESAS) on the 7th day; the follow-up will be performed on the 14th and 21st day after the first treatment. A trial flowchart is shown in figure 1.

Participants

Eligibility criteria

Inclusion criteria

The inclusion criteria are as follows:
1. Individuals aged \(\geq 18\) years.
2. Diagnosis of cancer by pathological examination.
3. Moderate-to-severe pain (NRS \(\geq 4\)) at an immobilised location.
4. Signed informed consent.

Exclusion criteria

The exclusion criteria are as follows:
1. Pregnant or lactating women.
2. Abnormal blood coagulation test results; low whole blood count; low platelet count; local skin lesions such

Figure 1  Trial flowchart. ESAS, Edmonton Symptom Assessment System; NRS, Numerical Rating Scale.
as burns, eczema, ulcers, frostbite ulcers; and other contraindications to acupuncture treatment.

3. Inability to cooperate with the treatment or evaluation.
4. Severe complications, such as severe arrhythmia or myocardial infarction.
5. Other conditions which the researchers consider as being ineligible in this study.

Recruitment and withdrawal
This study will screen for eligibility and recruit 120 participants at the Oncology Department of The First Affiliated Hospital of Guangzhou University of Chinese Medicine. Patients who meet the eligibility requirement will be informed about the trial before deciding whether they would like to participate. After informed consent, a statistician will randomly assign the patients via block randomisation into the treatment or control groups, with 60 participants in each group. The control group will have their pain treated with analgesic management alone, whereas the treatment group will have pain treated with FSN therapy in addition to analgesic management. Since FSN may be more effective for local pain treatment, we will limit recruitment to patients with immobilisation pain.

Sample size calculation
Based on our previous study, the opioid dose (morphine equivalent doses) per day in the treatment group is 64±43.56mg and 86.15±85.78mg in the control group. Therefore, we set α=0.05 and β=0.2; subsequently, we calculated the sample size as 60 per group using power analysis and sample size 11.0 (NCSS, Kaysville, Utah, USA).

Randomisation and blinding
The researchers will screen patients for eligibility, and recruiters will be responsible for recruiting 120 individuals. According to the principle of block randomisation, random numbers, generated using the Stata V.14.0, will be packaged and concealed in envelopes by a third-party statistician.

The participants and practitioners involved in this study will not be blinded. However, the researchers responsible for data collection from participants and statistical analysis will be blinded to the allocation assignment to minimise the bias of subjective outcome reports.

Intervention
Analgesic management
Both groups will be administered analgesic drugs according to the NCCN cancer pain guidelines. The medication will be administered every 12 hours. Physicians in the cancer department will calculate the dosage of OxyContin based on the patient’s pain severity and previous analgesic medication history.

In cases of acute outbreak pain, physicians will evaluate the nature of the pain and use related treatments. For pain unrelated to oncological emergencies, short-acting opioids with a rapid effect (dose: 10%–20% of the daily dose of opioids) will be selected. In addition, analgesia will be administered to prevent predictable outbreak pain, such as that elicited by dressing changes or activity. For outbreak pain caused by bone metastasis, adjuvant medications such as non-steroidal anti-inflammatory drugs will be considered. If pain is caused by oncological emergencies, the physician will take corresponding medical measures and institute analgesic management after diagnosis and evaluation. For example, it is recommended that new-onset back pain should be evaluated as spinal cord compression until plain radiography or MRI rules it out. Otherwise, patients should receive other medical measures, including steroid treatment, surgery and radiation therapy, to preserve their motor and sensory functions.

Acupuncture treatment
Certified acupuncturists with more than 3 years of acupuncture experience will provide FSN therapy. In addition, acupuncturists will be retrained to ensure the completion of the study.

The patient will be asked to indicate the most painful point, and the doctor will assess the level of muscle tension and other abnormal sensations (stiffness and spasm) by palpation. Furthermore, the doctor will assess the muscle-related joint’s range of motion and muscle contraction strength. Subsequently, the FSN will be inserted into the subcutaneous tissue at a position of approximately 5 cm around the location of pain, followed by sweeping and dispersing in all directions. Generally, the selected acupuncture point will be punctured with FSN once each time, and the needle will be fan-swept in the range of 30°–45° at a frequency of 50 times per min, lasting for 2 min. Next, based on the theory of reperfusion, the patients will be guided to perform isometric or isotononic muscle contractions for 10 s each time and repeat the reperfusion activities three times (figure 2). Finally, the doctor will withdraw the needle and leave the tube under the subcutaneous tissue, using a sterile transparent dressing to fix the tube for 3–4 hours. FSN therapy will be administered one time a day for 6 days.

Apart from FSN, any other therapies that may stimulate acupoints, such as transcutaneous electrical nerve stimulation, moxibustion and acupressure, will not be allowed during this trial.

Outcomes measurements
The evaluators will detect the outcomes at baseline, on the 7th day and during the follow-up period (table 1).

Primary outcome
Analgesic consumption
We will use analgesic consumption as the primary outcome. The use of opioids will be evaluated using morphine equivalents. For patients treated with opioids, 10mg of OxyContin is equivalent to 20 mg of morphine. The dosage of analgesics at the end of the treatment and
the total amount of analgesics used during the treatment will be compared between these groups.

Secondary outcomes

Pain degree

The NRS is a tool used to evaluate the degree of pain. The scale uses numbers from 0 to 10 to represent the degree of pain. A 1–3 score indicates mild pain in patients, indicating pain that does not considerably affect the quality of life. A score of 4–6 indicates moderate pain. A score >7 indicates severe pain.

Outbreak pain

We will record the frequency and number of pain outbreaks. Subsequently, when the treatment is completed, we will extract the patient’s daily outbreak pain information from the electronic medical record to calculate the frequency and degree of the patients’ pain during the outbreak.

Symptom assessment

Patients will be assessed for symptoms related to cancer pain using the ESAS. The ESAS includes the common symptoms of patients with cancer, such as tiredness, nausea, depression, anxiety and drowsiness. It is easy to use, and a higher score indicates worse symptoms.

Adverse events

In the case of an adverse event, its cause will be analysed to determine whether it is related to FSN or analgesics. The data will be included in the safety analysis.

Adverse reactions of FSN may include fainting, sticking of the needle, bending of the needle, instrument breakage and haematoma. The side effects of analgesics include constipation, nausea, vomiting, urinary retention, drowsiness, dizziness, confusion, opioid overdoses and poisoning.

Serious incidents will be immediately reported to the ethics committee, and the trial will be stopped to protect patients’ rights.

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<td>Interventions</td>
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Data management

Full-time staff at the research site will collect the data. Both electronic medical records and case report forms (CRF) will be used for data collection. Demographic and background medical variables will be obtained from the participants’ electronic medical records. In addition, the researchers will collect accurate individual data using a predesigned CRF.

After data collection, other staff members will reassess the CRF to confirm the information. When using the CRF, all modifications will be recorded. After the CRF is completed, the chief of the research site will lock it for safekeeping. After the follow-up, all original data will be digitised, and the original CRF will be sealed and stored until the unsealing period.

We will establish a data monitoring committee with responsibility for monitoring data quality. The data monitoring committee is a third-party independent of the researcher and sponsor and has no conflicts of interest with this study. The data monitoring committee will review the data every 6 months to ensure the data quality.

Statistical analysis

Professional statisticians will analyse the data. The use of analgesic drugs and the NRS score of pain degree will be statistically analysed using a mixed effect model. In addition, per-protocol analysis and intention-to-treat analysis will be performed for all outcome indicators to compare the results. P value<0.05 will be considered statistically significant. Statisticians will perform all statistical analyses using the R V.3.4.3 statistical software package.

Patient and public involvement statement

Patients and the public will not be involved.

Ethics and dissemination

All researchers will adhere to medical ethics during the trial. Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval No: K(2021)096). Before enrolment, the patients will be fully informed about the clinical trial, and the informed consent signature of all eligible patients will be obtained. All patients’ relevant data will be kept strictly confidential.

The Institutional Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine will be responsible for this study’s safety and quality control. Therefore, they can propose modifications to the research design to protect the participants’ rights, and the main investigator will make the final decision.

In the case of unexpected events, the research site will report it to the primary investigator within 24 hours and to the ethics committee for recording.

During each visit, information about this trial will be assessed, including the research plan, ethics approval, CRF, informed consent and other materials. For the CRF, it will be necessary to confirm that each patient’s name, identifier number, random number, sex, allocation of the intervention plan, adverse events, outcome indicators and other information are completed.

All individual data will be shared after de-identification. Other documents will be available as well, including the study protocol, statistical analysis plan and analytical code. Data accessibility will require approval by an independent ethics committee beginning 12 months after publication. Other researchers may request the data set by email to the corresponding author. There is no plan for the collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial or for future use in ancillary studies. The results of this study will be submitted for publication in peer-reviewed publications.

DISCUSSION

Approximately two-thirds of patients with cancer experience cancer pain during their illness. Although there are many guidelines for treating cancer pain, more than 30% of patients have uncontrollable symptoms. The serious adverse effects and potential addiction risks of opioids provide challenges in pain management. Therefore, complementary and alternative therapies have become increasingly popular for symptom control in clinical practice, leading to an acceleration in the development of integrative medicine. In contrast to conventional oncology care, integrative oncology aims to add evidence-based complementary and alternative therapies to the daily care of patients to address their physical and mental problems and improve their quality of life.

As a part of integrative oncology, FSN has been used in pain management to reduce the analgesic dosage needed by patients with cancer and to improve quality of life. However, the mechanism of FSN analgesia is not well understood. Fu indicates that myofascial trigger spots are fundamental to FSN, which is a consensus of FSN practitioners. Li et al believes that FSN can relieve pain by improving the skeletal muscle mitochondrial ultrastructure and function; however, the signal pathway is not fully understood. It was not until 2021 that Xu et al proposed the immune hypothesis for the mechanism of action of FSN. When the needle stimulates the subcutaneous tissue, tissue self-repair will stimulate the immune system. While participating in the repair of tissue, immune cells (leucocytes and plasma cells) also block the pathological factors of the original pain (interleukin and tumour necrosis factor, among others) to achieve the effect of pain relief. However, this immune hypothesis has not yet been tested.

The Society for Integrative Oncology-American Society of Clinical Oncology management guidelines on integrative medicine cancer pain suggests acupuncture may be offered to patients with cancer experiencing pain, particularly those with musculoskeletal pain. However, the evidence quality is intermediate. Similar to other acupuncture research, the level of evidence from the FSN study is not high because FSN study is also confronted with a blinding design challenge.
However, the design of sham acupuncture studies remains controversial. Some researchers suggest that sham acupuncture has only a placebo effect on patients. In contrast, others believe that it may cause a certain degree of stimulation and may have a possible therapeutic effect on the outcomes.\(^1\)\(^2\) Recently, non-blinded pragmatic trials have been recommended as they emphasise real-world effects and their results are propitious for application and promotion in clinical practice.\(^3\)\(^4\) Therefore, using real-world study methods may be one of the important directions for future FSN research. Acupuncture or integrative oncology can be promoted by advancing the FSN in this way. On one hand, innovative acupuncture procedures (battle-filed acupuncture and FSN) do not require doctors to learn traditional Chinese medicine. Relying on their existing knowledge background, they can quickly complete the innovative acupuncture procedure training and start serving patients with cancer. On the other hand, developing the innovative acupuncture procedure will also force self-improvement and the evolution of traditional acupuncture and align itself more with current clinical practice.

The advantages of our study design include the following: first, our pragmatic trial design will be more suitable for real-world clinical practice. Second, we will design and conduct this trial rigorously to evaluate the effect of FSN in relieving cancer pain. Third, according to the NCCN, we can effectively protect the rights and interests of patients by adding FSN therapy to their analgesia management. Fourth, we will focus on the pain of patients and the impact of pain, including the use of analgesics and changes in pain-related symptoms, which will be valuable to clinical practice.

This study has some limitations. First, this trial will be conducted in China; therefore, the applicability of the results to other populations needs to be considered carefully. Second, patients may be unintentionally biased when reporting to outcome assessors due to the open-label design. This should be taken into account when interpreting the results of the study. Third, this is a pragmatic randomised controlled trial; therefore, other ‘real-world’ factors may influence the data and its interpretation. We will interpret our results carefully with these limitations in mind.

**Author affiliations**

1. Rehabilitation Center, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
2. Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
3. Oncology Center, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
4. Radiotherapy Department, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
5. Acupuncture Department, Guangdong Provincial Hospital of Chinese Medicine (The Second Affiliated Hospital of Guangzhou University of Chinese Medicine), Guangdong Provincial Academy of Chinese Medical Science, Guangzhou, Guangdong, China
6. Oncology Department, Guangdong Provincial Hospital of Chinese Medicine (The Second Affiliated Hospital of Guangzhou University of Chinese Medicine), Guangdong Provincial Academy of Chinese Medical Science, Guangzhou, China

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**Competing interests** None declared.

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**Patient consent for publication** Not applicable.

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**ORCID iDs**

Yang Cao http://orcid.org/0000-0003-3230-5346
Yihan He http://orcid.org/0000-0002-4833-0231

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