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STUDY PROTOCOL

REVISED The efficacy of acupuncture as a complementary treatment for pain and anxiety after breast cancer surgery: Study protocol for a pragmatic randomized control trial [version 2; peer review: awaiting peer review]

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Abstract

Background: Breast cancer is one of the most prevalent cancers worldwide. Fortunately, survival has improved in recent years thanks to its early detection and curative treatments such as mastectomy. However, this medical procedure is associated with a range of unwanted effects such as postoperative pain and anxiety. Some studies have reported that acupuncture could be an effective treatment to control these types of symptoms, although only few studies have been conducted on women undergoing mastectomy.

Methods: This is a pragmatic randomized controlled trial with blind assessors. The study will be conducted in the Breast Unit of Hospital Universitario Sagrado Corazon of Barcelona (Spain). A sample of 40 women will be recruited and randomized to receive acupuncture treatment in addition to standard care procedures, or standard care procedures alone. The main outcome, pain, will be assessed after the surgical intervention and 4, 10 and 30 days later using the numerical rating scale. Secondary outcomes include anxiety, use of analgesics, nausea, adverse effects, and surgical complications.

Discussion: Acupuncture is a low-cost non-pharmacological strategy. This study will help to clarify its possible role in controlling post-mastectomy adverse effects.

Trial registration: ClinicalTrials.gov [NCT04608175](https://clinicaltrials.gov/ct2/show/study/NCT04608175) 29/10/2020

Keywords

acupuncture, breast cancer, pain, anxiety, randomized control trial

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Abbreviations

NRS: Numerical Rating Scale

HADS-A: Anxiety subscale of the Hospital Anxiety and depression scale

Background

According to the latest report of the Spanish Medical Oncology Society, breast cancer is the second most prevalent cancer worldwide and the fourth most prevalent in Spain, with a total of 32,825 new cases in 2018. It is the most frequent cancer in women, and one out of every eight women will suffer from breast cancer at some time during their lifetime¹. Despite this, survival from breast cancer is over 80% in non-metastatic patients, largely due to early detection programs and advances in its treatment².

Breast surgery is one of the commonest treatments for breast cancer and is used in most cases³, although it is not free from unwanted effects. One of the most frequent complications after breast cancer surgery is post-operative pain. Around 65% of patients undergoing breast surgery experience significant pain at discharge of around 6 points on the numerical rating scale. This lasts up to one month in 26% of cases⁴ and becomes chronic in around 25% of patients⁵. In addition to pain, patients also experience other adverse effects such as anxiety, nausea, and fatigue, all with serious consequences on quality-of-life and an increased use of healthcare resources⁶.

Acupuncture is a non-pharmacological treatment that involves the stimulation of specific points on the body surface by inserting needles. Although not a standard hospital procedure, several studies in recent years have shown acupuncture to be useful at controlling post-operative pain and reducing opioid intake and symptoms of nausea and vomiting⁷⁻¹⁰.

Two important studies have been carried out on the use of acupuncture in women undergoing surgery for breast cancer. The first corresponds to a feasibility study with no control group conducted in 2008 at the Mayo Clinic. This study, carried out on a sample of 24 patients, found that applying acupuncture in a hospital setting in women after breast cancer surgery was a feasible treatment option, and reported significant reductions in pain, anxiety and muscle tension and discomfort¹¹. The second study, a pilot randomized controlled trial also carried out in the U.S., compared the effects of acupuncture with those of routine treatment in 30 women undergoing mastectomy. This trial not only found acupuncture to be a feasible treatment option, but also observed a reduction in pain, nausea and anxiety compared to the control group¹². Despite the findings of these two trials, there is only limited evidence for the potential benefits of using acupuncture in these patients and further research is required before it can be incorporated in routine clinical practice.

The aim of this study is to establish the efficacy of acupuncture treatment administered in addition to conventional treatment to control post-operative pain.

Study design

Pragmatic randomized controlled trial with blinded assessors at a ratio of 1:1.

Methods

Main objective

To determine the efficacy of acupuncture treatment in addition to conventional treatment to reduce post-operative pain.

Secondary objectives

1. To determine its efficacy at reducing levels of anxiety.
2. To determine its efficacy to reduce nausea and vomiting.
3. To determine its efficacy to reduce rescue analgesic medication use.
4. To determine possible adverse effects of acupuncture.
5. To determine possible changes in the incidence of post-operative complications (seroma, problems with wound healing etc.)

Study setting

This study will be carried out in the Breast Unit of the Hospital Universitario Sagrado Corazon in Barcelona

Ethics approval and consent to participate

This protocol was approved by the research ethics committee of the Hospital Universitario Sagrado Corazon of Barcelona (identification code: 2019/59-FIS-HUSC). The committee will be immediately notified about any change made to the protocol.

All patients will be informed of the nature of the study, its objective, and the possible adverse effects of the treatments, as well as their voluntary participation. All patients must sign an informed consent document. The patients will be able to leave the study whenever they want without this affecting their health care in any way.

The data collected during the study will be treated in accordance with the LOPD, Regulation (EU) n°2016 / 679 of the European Parliament and European Council on data protection (RGPD) that came into force on May 25, 2018.

Data monitoring is not needed as the treatment used is expected to have low safety risk. For the same reason, no interim analysis or stopping guidelines are considered. No additional insurance was needed for this trial.

This study was registered with ClinicalTrials.gov on 29th October 2020 ([NCT04608175](https://clinicaltrials.gov/ct2/show/study/NCT04608175)).

Participants

The study participants will be women diagnosed with breast cancer (as primary cancer) undergoing mastectomy. The participants will be recruited from the Breast Unit of the Hospital Universitario Sagrado Corazon in Barcelona by the head physician in the Unit in accordance with the following inclusion criteria: 1- Diagnosis of breast cancer. 2- Primary

breast cancer patient, 3- Candidate for breast cancer surgery (mastectomy), 4- Aged between 20 and 70 years old, 4- Consenting to participate in the study and signing the informed consent form. Patients will be excluded from participating in the study if they: 1- Have a previous history of breast cancer, 2- Have a previous diagnosis of a severe psychiatric disorder, 3- Severe neutropenia, 4- Do not speak Spanish or Catalan, 5- Are currently receiving acupuncture treatment or have received it in the last month, 6- Are currently participating in another trial.

Interventions

Acupuncture group (experimental). The experimental group will receive the standard treatment administered in these cases (analgesic regimen and nursing care procedures), in addition to the following acupuncture therapy.

In the first visit (preoperative), the anamnesis and energy diagnosis of each patient will be carried out following the practices of Traditional Chinese Medicine (TCM) to design a personalized treatment based on the patient's medical history. The diagnosis will be made following the 5 elements Theory (Wu Xing) and the theories of Yin/Yang and fundamental substances (Qi, Xue, organic liquids), reaching diagnoses such as "Insufficient Yin of Wood" or "Insufficient Qi of Earth"¹³. A treatment of approximately 10 to 12 acupuncture points will be designed considering the TCM diagnosis and medical history of each patient. Both TCM diagnosis and the points used will be reassessed in each session.

For the treatment, the patients will lie on a bed in the most comfortable position possible. The punctured sites will be disinfected with alcohol. After insertion of the needles, manual stimulation will be performed to obtain the "De Qi" sensation using twisting and lifting and thrusting manipulations and the needles will be left in place for 30 minutes. The points belonging to the upper extremity of the affected breast will be treated on the contralateral side, taking care not to insert any needle in the limb on the affected side. No points in the operated region will be used.

As recommended by the STRICTA guidelines (Standards for Reporting Interventions in Clinical Trials of Acupuncture), the ranges and means of the number of needles and points used will be reported in the study results¹⁴.

The acupuncture treatment will be carried out by a physiotherapist with a master's degree in Traditional Chinese Medicine-Acupuncture (60 credits) and 6 years clinical experience in an acupuncture setting.

The treatment will be administered with disposable surgical steel acupuncture needles (from Zen Long) of 0.25 × 25 mm and 0.25 × 13mm with silver-coated copper handle and rounded head. Also, permanent surgical steel auricular needles of 0.22 × 1.5 mm with adhesive tape (from Zen Long) will be used.

Control group

The control group will only receive standard care procedures (analgesic regimen and nursing care procedures), although

they will have the same follow up visits as the patients in the intervention group to facilitate analysis of the study variables.

Only acupuncture treatment in the control group will be prohibited during the trial.

Outcomes

The assessor recording the study outcomes will not know which group the participants have been assigned to. For this purpose, the acupuncture treatments will be carried out in a closed room.

Main study outcome

Pain. Pain will be evaluated using the numerical rating scale (NRS)¹⁵. This measure uses a scale of 0 to 10 in which the higher values represent the most severe pain. The NRS has been validated for numerous populations and is considered to be reliable and easier to use and to understand than the visual analogue scale (VAS)¹⁶. Pain will be assessed at three different time points: 12 hours after surgery (before the acupuncture treatment), 48 hours after surgery (after the acupuncture treatment), in the first out-patient visit between 10 and 12 days after the intervention (evaluated after the acupuncture session), and one month after surgery (evaluated before the acupuncture session).

The analgesic medication administered to each patient after the intervention will be recorded in detail both during the hospital stay and in the patient's home until day 15 after surgery.

Secondary outcomes

Anxiety will be evaluated by the Spanish version of the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A)¹⁷. Evaluations will be made 12 hours after the intervention, at 48 hours, between 10 and 12 days later and one month after surgery. In the preoperative visit, all patients will complete the anxiety questionnaire, which will provide the baseline data.

The intensity of postoperative nausea will also be evaluated by the NRS¹⁸ at 12 hours and at 24–48 hours after surgery.

Adverse events possibly linked to acupuncture such as pain, hematomas etc. will be after each acupuncture session and follow up session

Post-operative complications such as seroma, infection and wound healing will be recorded in each follow up session.

- Sociodemographic variables:

At the time of inclusion, in addition to the study variables the sociodemographic variables (age, race, ethnicity, education level, civil status, tumour type, treatment before or after the intervention) will also be recorded.

Participant timeline

Participant timeline is described in [Figure 1](#).

TIMEPOINT**	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
	-t ₁	0	Day 1 pre QI	Day 1 Post QI	Day 4 post QI	Day 10-12 post QI		1 month post QI
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Intervention			X		X	X		
Control								
ASSESSMENTS:								
Pain				X	X	X		X
Analgesic medication					X	X		
Analgesic medication				X	X	X		X
Nausea				X	X	X		
Anxiety			X		X	X		
Adverse events					X	X		X

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158:200–7.

Figure 1. Schedule of enrolment, interventions, and assessments.

Randomization sequence and assignment to study groups

Participants will be randomly assigned to the study groups. The main investigator will use a computer generated randomized list, to which only he/she will have access via a password. The remaining investigators will be blinded to patient assignment.

After obtaining a written informed consent from each patient (extended data¹⁹), the individual responsible for recruitment will enter the patient's data on an Excel flat-file table. The principal investigator will then use these data to generate the randomized list. This procedure will be continued until the data for all the patients have been entered.

Patients will be informed that they will be randomly assigned to one group or the other and their levels of pain and anxiety will be evaluated and filled in a collection sheet (extended data¹⁹).

Blinding

For practical reasons, neither the participants nor the physiotherapists administering the acupuncture will be blinded. However, the remaining investigators participating in the study

(responsible for recruitment, evaluation, and statistics) will be blinded.

Size of the study sample

The sample size has been calculated considering a value of 2 points in the NRS, used in previous studies²⁰, as a clinically significant difference, and a standard deviation of 1.99¹¹. Finally, an Alpha risk of 0.05 and a Beta risk of 0.2 in a bilateral contrast was considered. The estimated sample size is 40 subjects (20 per group). Loss to follow up has been estimated to be around 20%. To reach this target sample size, two centres will be participating in this study.

Statistical methods

For the statistical analysis **SPSS** Statistics software will be used. For the descriptive analysis of the sociodemographic data, means and standard deviations will be used for the continuous variables and absolute values and percentages for the qualitative variables.

For the comparative analysis, mean difference will be used with a confidence interval of 95%, calculated by the Student-t or Mann-Whitney U tests, depending on the distribution of

variables. Differences will be considered significant with values of $p < 0.05$.

Intention-to-treat analysis will be carried out. In case of missing data, last value carried forward methods will be used. In case of significant baseline differences between the two groups, there will be an adjusted analysis for these outcomes.

Adherence strategies

To encourage participants to attend the follow up session one month after the intervention, all participants (in both the treatment and the control group) will be offered an extra acupuncture session. This will take place after the final assessment, so its effects will not affect the study results.

Dissemination of information

Results of the trial will be disseminated via publication. Authorship eligibility will be considered in accordance with the International Committee of Medical Journal Editors criteria. A professional writer will be used to review the final manuscript.

Study status

Recruitment will begin in November 2020 and is estimated to have been completed by November 2022.

Discussion

The aim of this study is to determine the value of acupuncture as a complementary treatment to the conventional treatment administered to women undergoing mastectomy. Owing to the pragmatic design of the study, it will not be possible to determine whether the effects observed are due to specific or non-specific effects of the treatment. However, we will be able to determine the efficacy of this technique in a context similar

to real clinical practice. With the same objective, the acupuncture treatment has not been prespecified, but will be based on the specific diagnosis of each participant following standard acupuncture procedures.

Data availability

Underlying data

No data are associated with this article

Extended data

Figshare: The efficacy of acupuncture as a complementary treatment for pain and anxiety after breast cancer surgery extended data. <https://doi.org/10.6084/m9.figshare.13298918>¹⁹

This project contains the following extended data:

- Consent form.pdf (Participants consent form)
- Data collection sheet.pdf (Study data collection form)
- Registration dataset.pdf (World Health Organization Trial Registration Data Set)

Reporting guidelines

Figshare: SPIRIT checklist for 'The efficacy of acupuncture as a complementary treatment for pain and anxiety after breast cancer surgery: Study protocol for a pragmatic randomized control trial' <https://doi.org/10.6084/m9.figshare.13298918>¹⁹

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