

BMJ Open Randomised clinical trial of a manual therapy programme to reduce the evolution time of axillary web syndrome in women affected by breast cancer: study protocol

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ABSTRACT

Introduction Breast cancer is the most common malignant tumour in women, with more than 2 million new cases annually worldwide. One of the most frequent and well-known surgical and post-actinic sequelae is post-mastectomy lymphoedema. The axillary web syndrome is another sequela that limits the functionality of the patient and delays the protocol time of administering cancer treatments; and in many cases, this sequela is misdiagnosed. This surgical sequela usually disappears spontaneously after the third month of appearance, but this implies a long period of discomfort and limitations for the patient, at the same time, it may delay the application of radiotherapy within the indicated protocol deadline (due to a need for body posture).

Methods and analysis With the present quasi-experimental study, we intend to show the application of physiotherapy and stretching from the beginning of the appearance of the axillary cord, in a controlled and scheduled way by the physiotherapist. It is possible to reduce the time in which the lymphatic thrombus is present and, therefore, recover functionality and mobility, reduce pain and be able to apply treatments within the established deadline. We intend to apply this therapy into the intervention group and compare thrombus evolution time with the control group.

Ethics and dissemination This trial has the approval of the Andalucía Ethics Committee (PEIBA code 1909-N1-21, reg. number 171.21).

Trial registration number ClinicalTrials.gov Registry (NCT05115799).

INTRODUCTION

Breast cancer is the most common tumour in women around the world and it is one of the leading causes of death among women in developed countries.¹ It is an important public health issue, since according to the WHO, more than 2 million new cases are diagnosed annually worldwide, becoming almost a quarter of malignant tumours in women.² In the Western world, it has been

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The comparison of the traditional treatment strategies with this novel treatment proposal could demonstrate a new tool within physiotherapy to manage this health problem.
- ⇒ The Spanish healthcare system is free with equal access for all patients, which prevents selection bias.
- ⇒ This study is carried out in a specific unit with numerous patients who suffer from breast cancer. Due to this number of patients, it is not difficult to achieve the sample size required.
- ⇒ Due to the nature of the intervention, blinding is not feasible for participants or assessors.
- ⇒ The few studies related to this subject conclude that more clinical trials like this one are necessary in order to have a physiotherapeutic treatment strategy in lymphatic thrombus.

shown that 1 in 9–12 women will suffer from this disease in her lifetime.³

Most cases occur in postmenopausal women and the main age at diagnosis is around 60 years.⁴

After the diagnosis of breast cancer, the patient normally undergoes surgical and/or cancer treatment. Chemotherapy, radiotherapy and hormonal therapy are some of the treatment alternatives which are currently adapted with precision to the type of tumour in order to achieve a better response and survival.⁵

Post-mastectomy lymphoedema is one of the best-known post-surgical and post-actinic sequelae after breast cancer, with a prevalence of around 20% in mastectomised women.⁶ The conservative treatment of this health issue is based on decongestive physical therapy and physiotherapy.^{7,8} Pneumatic

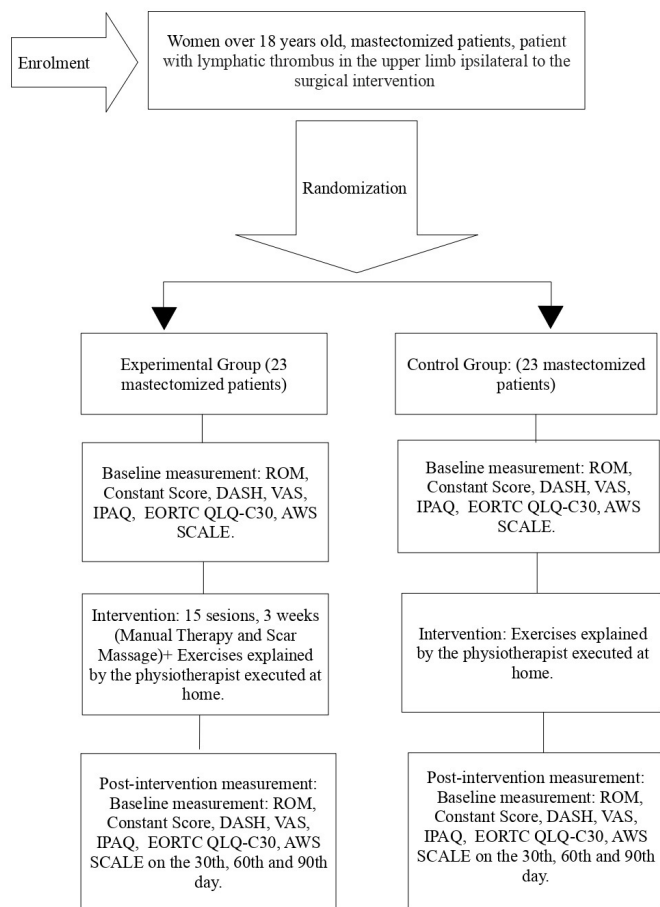


Figure 1 Study design. AWS, axillary web syndrome; DASH, Disabilities of the Arm, Shoulder and Hand; IPAQ, International Physical Activity Questionnaire; ROM, range of motion; VAS, Visual Analogue Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality Life Questionnaire Core 30

multicompartmental pressotherapy helps reduce the feeling of heaviness and stiffness of oedema.⁹

In addition to post-mastectomy lymphoedema, the patient undergoing surgery for breast cancer may present with axillary web syndrome (AWS) or superficial lymphatic thrombosis. As described by Yeung *et al* in their systematic review,¹⁰ AWS can appear in the first 8 weeks after the operation and usually resolves spontaneously within 3 months of its appearance.¹¹

The lymphatic thrombus is clinically manifested as a cord that frequently occurs in the armpit, although it can also appear along the upper limb, elbow crease and even reaching the first finger.^{11–13} Regarding the diagnosis through imaging tests, nuclear magnetic resonance does not manage to clearly identify the AWS. Ultrasound, on the other hand, is the most reliable method as it allows movement to the patient's arm while the diagnostic test is being carried out.^{12 14}

The AWS produces pain when abducting and flexing the shoulder with the respective loss of functionality and limitation of mobility of the affected upper limb.¹⁵

According to the American Cancer Society, radiation therapy is applied 3–8 weeks after the operation if chemotherapy is not required. If chemotherapy is used, it is applied 3–4 weeks after completion. It is usually applied 5 days a week from Monday to Friday.

The limitation of mobility often leads to a delay in the application of this useful tool in the oncological therapeutic arsenal to prevent recurrences,^{16–18} hence, the need and importance of this study, in which we intend to demonstrate that the development time of lymphatic thrombus can be reduced with assisted passive stretching.

The frequency of the AWS is not clear from the current publications. It depends on the type of surgical intervention, age, body mass index (BMI),¹⁹ the appearance of the postoperative seroma and even breast reconstruction,²⁰ thus, being 30% the frequency in the operated patients.^{11 21}

After reviewing the relevant literature, it should be noted that there are very few studies and therefore little evidence on the treatment of AWS. It is not possible to prescribe a clear treatment in a clinical practice guide for this post-surgical sequela. Most publications highlight the importance and need for more research to determine aetiopathogenesis and useful treatment for this health issue.^{10 13}

Objectives

The main objective of this research is to determine a preliminary exploration of the magnitude of the effect through physiotherapy and stretching intervention for the functional recovery of the upper limb, as well as the recovery of the surgical scar and the improvement of the quality of life of women who have suffered from breast cancer.

The secondary objective is to create a scale to objectively classify the axillary thrombus (based on its clinical manifestations).

METHODS AND ANALYSIS

This is a randomised clinical, prospective study. This research uses the guidelines on Standards for Quality Improvement and Excellence in Reporting and Consolidated Standards of Reporting Trials (CONSORT).²²

The Standard Protocol Items: Recommendations for Interventional Trials checklist is provided in the [Figure 1](#), and the flow diagram for the study protocol is included in [figure 1](#). The research procedure was approved by the Andalusian Ethics Committee on Human Research (PEIBA code 1909-N1-21, reg. number 171.21).

Participants

The study includes people undergoing surgery for breast cancer who attend the lymphoedema unit of the A G S Campo de Gibraltar West and presenting with lymphatic thrombus after surgery. The recruitment period extends from October 2021 to October 2023. Patients who meet

all the inclusion criteria and no exclusion criteria will be included in this study prospectively.

Inclusion criteria

Adult patients, mastectomised patients (either radical or conservative surgery) and patients with lymphatic thrombus in the upper limb ipsilateral to the surgical intervention. The thrombus must be visible and palpable. It must limit the mobility of the arm and it must be more apparent when abducting the arm.

Exclusion criteria

Patients will be excluded if they have any significant psychological and neurological alterations that would prevent the retrieval of the necessary information for the investigation. Moreover, patients will be excluded if they have a legal dispute that would affect their intervention in this study, and finally, patients suffering from metastasis who are not treated with chemotherapy treatment will also be excluded.

Withdrawal criteria

An administrative decision taken by the researchers, promoter or a regulatory authority; a mild adverse event; a serious, unexpected or clinically relevant adverse event or the withdrawal of informed consent from the patient.

Recruitment procedures

All patients with lymphatic thrombus in the study period who attend the lymphoedema unit of the A G S Campo de Gibraltar West are included. They must meet the inclusion criteria.

The day a patient comes to the clinic with the thrombus, a clinical assessment is made and it is checked whether she belongs to the control group or the intervention group. If she belongs to the control group, she is advised to perform exercise daily, as is done in current clinical practice in patients with this health problem. If she belongs to the intervention group, the treatment described below begins the next day.

Randomisation procedures and blinding

Randomisation will be carried out with the Excel program and the 'randomisation' tool.

A list of numbers from 1 to 46 (number of patients in the clinical trial) will be randomly assigned to either a control group member or intervention group member through the aforementioned tool (23 patients in each group). When a patient arriving at the consultation suffers from AWS, she will be assigned a number in the order of her arrival. The given number is checked against the randomised Excel list in order to confirm whether the number belongs to either the control group or intervention group.

The study is not blinded because the patient can see if she belongs to the control group or the intervention group. The manual physiotherapy intervention does not allow for blinding.

Intervention

Fifteen assisted passive stretching sessions of 40 min each will take place. These are facilitated 5 days a week for 3 weeks by the physiotherapist.

Sessions will start with pendular shoulder exercise to warm up and offer proprioceptive stimulus to the patient's joint capsule.

Stretches applied during the sessions will be gentle and maintained, never exceeding a pain grade of 6 (moderate pain) in the Visual Analogue Scale (VAS). Once the cord tension is reached, it is maintained. In most cases, the cord is found in the axillary area; therefore, this is the area where the stretching will be focused on.

In case the cord reaches the elbow crease, this area will also be treated in supination and extension of the elbow. In case the cord reaches the hand, the desired position will be ulnar deviation together with opposition of the thumb.

Scar massage will be performed on the axillary scar to dislodge underlying planes and the subcutaneous tissue of the muscle fascia, never exceeding a pain grade of 6 (moderate pain) in the VAS.

Requirement to treat the scar with a scar massage: surgical stitches must be removed, there must not be signs of infection and the scar must be healed. If all of these conditions apply, scars will be treated, whether they are attached to underlying tissue or not.^{23 24}

The patient will be trained in active exercise to prevent lymphoedema and activate lymphatic circulation. The patient will also be trained with hygienic-postural measures for the same purpose.

Those patients suffering from lymphoedema, as well as AWS, will receive complete decongestive therapy to treat lymphoedema once they finish the sessions described in this study. Therefore, complete decongestive therapy to treat lymphoedema does not contaminate the procedures described through the study. Those patients who do not suffer from lymphoedema will not receive complete decongestive therapy (see online supplemental annex 1).

Usual care (control) group

The physiotherapist advises patients on how to perform stretching exercise for lymphatic thrombus while it is present. All control group patients will be instructed in hygienic-postural care and active assisted auto-stretching to be performed daily for 30 min.

The stretches are described below:

- ▶ The patient opposite the wall raises her arm touching the wall slowly, for as long as her axillary thrombus permits. Once she has reached the maximum movement, she will hold that position for 20 s. She will then slowly lower her arm.
- ▶ The patient sits on an office wheeled chair, then rests her elbows on a table and the patient slides the chair backwards. There is a flexion of the shoulders. Once the maximum movement is reached, the stretch is maintained for 20 s. She will slowly return to the starting position.

- ▶ The patient stands, locks her fingers, keeps her elbows straight and flexes her shoulders to the maximum movement. Her healthy arm pulls on the arm with the lymphatic thrombus. The position of maximum flexion is maintained for 20 s and slowly returns to the initial position.
- ▶ During the development of the exercise, the patient must consider her correct postural correction.
- ▶ It will be assessed every 30 days. They also attend group therapy to reinforce learning.
- ▶ This is also explained to the patients in the intervention group (see online supplemental annex 2).

Outcome assessment

At first, the user's administrative data are collected: age, marital status, employment status, educational level, if the patient has ever become a mother and when. Regarding lifestyle, the patient is asked if she does practice sport and how often. It is also asked whether she lives in an urban or rural area. Smoking is also considered for the study. Regarding medical records, the following information is collected: BMI, type of tumour, date of first symptoms of AWS, number of lymph nodes removed, measurement of the circumference of both limbs, whether surgery done was radical or conservative, whether the patient has received radiotherapy, and finally whether the patient received breast reconstruction or not.

Axillary cord syndrome

It is a nominal qualitative variable. The presence of lymphatic cord will be assessed by observation and palpation by the assessor. Physical examination will be performed as suggested in previous researches: patient lying in supine position with elbows extended and the shoulders in maximum abduction. The assessor observes and palpates the cord, including the armpit, down the upper arm from the armpit to the antecubital space and through the forearm to the base of the thumb.¹⁰

Range of motion

It is a continuous quantitative variable. For the assessment of mobility, goniometry will be used. Goniometers are the standard instrument for measuring the range of movement. The patients will be asked to move their arms in flexion, extension, abduction and external and internal rotation of the shoulder. Maximum range of motion for the flexion and abduction is expected to be 180°; for extension 45°; 100° for internal rotation and 80° for external rotation.

Constant Scale

According to the Spanish Society for Shoulder and Elbow Surgery, the Constant Scale assesses pain, functionality for daily life activities, joint mobility and shoulder strength. Constant Scale also takes into account the laterality and time since surgery. The score ranges from 0 to 100 points, 100 being the optimal condition for the shoulder.²⁵⁻²⁷

Quick-Disabilities of the Arm, Shoulder and Hand

The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a specific instrument for measuring the quality of life related to health problems to the upper limbs. DASH is validated in Spanish and it consists of 30 questions. The final score calculation is relatively complicated. In order to calculate the scores, it is necessary to answer at least 27 of the 30 questions. The final scores are obtained by calculating the arithmetic means of the questions answered minus 1, multiplied by 25. The DASH questionnaire has excellent reproducibility and high sensitivity, being able to detect small changes. The scale ranges from 30 to 150 points: 30 means good shoulder functionality and 150 means non-functional shoulder.

It has two optional subsections where sports and work functionality can be assessed as well.²⁸

Visual Analogue Scale

According to the National Cancer Institute, it is a tool used to help professionals assess the intensity of certain sensations and feelings, such as pain. The VAS for pain is composed of a straight line on which one extreme means no pain and the other extreme means the worst pain imaginable. Extreme pain corresponds to 10 points. No pain corresponds to 0 points.

The patient marks a point on the line that matches the amount of pain felt.²⁹

International Physical Activity Questionnaire

The main worldwide use of the International Physical Activity Questionnaire (IPAQ) is aimed at monitoring and investigating. It is an instrument designed mainly for the 'monitoring' of physical activity performed by the adult population and their perception of their own health.

Its aim is to learn about the kind of physical activity that people perform as part of their daily activity. The questions are focused on the time the patient has spent being physically active during the previous 7 days. The patient should consider the activities he/she has been doing whether it is work, gardening, household chores, leisure, moving from one place to another during rest, exercise or sport.³⁰

EORTC-QLQ-C30 questionnaire

It consists of a validated questionnaire consisting of 30 questions. The first 28 questions are scored from 1 to 4, with the highest values being those that show greater difficulty when carrying out the activity for which they are asked or the worst state of health. It is not recommended adding up all items within the entire questionnaire.³¹

At the end of the questionnaire, there are two questions about the general state of health and quality of life that score from 1 to 7, with the highest value being the best state of health and quality of life. All questions refer to the previous week.

Data collection procedure and management

Study patients will be instructed in hygienic-postural care and active assisted auto-stretching to be performed daily

for 30 min. It will be assessed every 30 days (see online supplemental annex 1).

Control group

All the variables and data for each patient are recorded in their clinical history.

Goniometric study will be performed on the affected upper limb (shoulder, elbow, wrist).

Constant Scale, Quick-DASH, VAS and IPAQ will also be used. The assessment will be carried out when the patient arrives at our unit and on the 30th, 60th and 90th day.

Intervention group

Similar to the control group, all the variables and data from the intervention group will be collected in their respective medical history. Goniometric study of the affected upper limb will be performed (shoulder, elbow, wrist) to the aforementioned intervention group. Constant Scale, Quick-DASH, VAS and IPAQ will also be completed. This exploration will also take place during the first session and on the 30th, 60th and 90th day.

Statistical analysis

The results of the research will be presented as a summary of the outcome measures taken together with the estimated effect size and its precision. The statistical analysis will be performed according to the intention-to-treat principle using SPSS 27.0 software.

A descriptive analysis of all the variables included in the study will be presented in general overview and more specifically for both groups of the clinical trial. For the qualitative variables, the relative and absolute frequencies will be presented. In the case of such quantitative variables, summary statistics will be presented (mean, median, mode, minimum and maximum).

For all study objectives in which two qualitative variables are related, the non-parametric X^2 test will be used and, if necessary, the Fisher's test will be used (in cases where the absolute frequency of more than 20% of the levels is less than five observations). To quantify the possible predisposing factors, the relative risk measures, OR and their associated CI will be obtained; likewise, the sensitivity or specificity will be presented if it is considered necessary. All analyses will be accompanied by graphic representations for greater detail. Missing values will be those that are not completed. All analyses will be carried out with free R software and the significance level for all hypothesis testing is determined at 0.05.

The necessary sample size was calculated in order to detect, with a statistical power of 99%, a reduction on the remission time, from 12 to 2 weeks.

Considering an SD of 8 weeks in the control group and 4 weeks in the intervention group, we take into account a confidence level of 95% and lost to follow-up of 20%.

Therefore, according to the above parameters, 46 women would be needed in total: 23 in the intervention group and 23 in the control group.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. When the study is completed, the research team will send results, via email and by meetings, of the study to all participants and also to the organisations involved.

RESULTS

Enrolment began in October 2021 and is expected to end in October 2023. The research is planned to study 46 mastectomised patients with lymphatic thrombus. The absence of adverse effects could allow this treatment regimen to be the physiotherapy treatment of choice for AWS.

Primary outcomes: if the results confirm the expected benefits—which are mobility improvement and pain reduction—the quality of life of our patients will improve significantly. In addition, the patient will be able to receive cancer treatments without chronological delays due to mobility limitation in her arm.

Secondary outcomes: the development of the AWS classification scale will help to determine in detail the type of lymphatic thrombus, its location and its clinical characteristics.

This study could add more clinical evidence in the application of new physiotherapy strategies in the treatment of AWS. In the same way, it could reduce the time of evolution of this surgical sequela.

Ethics and dissemination

Institutional review board statement

The fundamental ethical precepts according to the Helsinki Declaration and Law 14/2007 of 3 July on Biomedical Research will be respected, guaranteeing the protection and confidentiality of data. Only researchers will have access to the data. The information collected from each subject will be associated with a numerical identification code, only identification of the patient for the purposes of data processing and analysis. This trial has the approval of the Andalucía Ethics Committee (PEIBA code 1909-N1-21, reg. number 171.21). Patients in the study are required to read and approve the consent form by signing the previous information for patients and the consent form (see online supplemental annex 3). Trial registration: NCT05115799 (ClinicalTrials.gov; accessed on 30 October 2021). This study will be carried out in accordance with CONSORT criteria.

Informed consent statement

An informed consent form has been prepared, which must be signed by all the subjects participating in the study who have previously received sufficient information about the objectives and procedure of the study. They will also be informed of the possibility of revoking the consent given at any time without having to justify their decision and without prejudice. All necessary permits will be requested from the institutions for the development of the research.

The research team will request the informed consent of the subjects be referred to in the research project (see online supplemental annex 3).

Data availability statement

The researcher declares that he follows the protocols of his work centre regarding the publication of data in accordance with the provisions of Organic Law 15/1999, of 13 December, on the Protection of Personal Data, and that the data will be incorporated into a file for the purpose of carrying out this research project. Participating subjects will be informed of the possibility of exercising their rights of access, rectification, cancellation and opposition of their data at the email address provided by the principal investigator.

Dissemination

1. Publication in journals indexed in the Journal Citation Report, in the field of Oncology and Rehabilitation and Physical Medicine and Physiotherapy.
2. Dissemination of results in national and international Congresses of Oncology and Rehabilitation and Physical Medicine and Physiotherapy.
3. Dissemination to the public, press releases and explanatory brochures of the project.
4. Dissemination on the website of the A G S Campo de Gibraltar West.

DISCUSSION

At present, there are some publications that show possible alternatives of physiotherapy treatment for lymphatic thrombus. Many are interventions with a very small sample (even on a case-by-case basis).^{32 33} Other studies are observational studies or are studies published longer than 5 years ago. There are some studies that combine manual lymphatic drainage (Vodder method) with physical therapy (strengthening, stretching, soft tissue work) with good results.³⁴

There is ambiguity in the association between the appearance of lymphatic thrombosis and lymphoedema of the ipsilateral limb. Patients who have developed AWS are 44% more likely to develop post-mastectomy lymphoedema.^{32 33} On the other hand, there are other studies that do not find a relationship between the two.³⁵

There are clinical trials with a design and patient sample similar to ours. The difference is that in their intervention group, manual lymphatic drainage is applied to patients with AWS together with stretching (regardless of the presence of lymphoedema); thus, some improvement regarding functionality and evolution time is found.³³

Other trials deal with the application of physical therapy, exercise and stretching for AWS, but excessive exercise can worsen AWS although it improves chronic pain.³⁶ Hence, we have emphasised the importance of specifying the exercise and work time in our study.

There are also some clinical trials where there could be a conflict of interest.³⁷

The methodological quality of our study would be higher if it had some blinding. For future research, the existence of single or double blinding would be recommended to improve the methodological quality of the clinical trial. In addition, further patient follow-up where possible recurrence of AWS, lymphoedema or some other health problems, and possible association with AWS, should be considered.

Contributors All authors have made significant contributions to the article. JBGR, RMV, CGM and MJVG coordinated the project, contributed to the conception and design of this study, and composed this current article. RMV and MJVG were responsible for methodological guidance. JBGR was responsible for developing the intervention and control protocols and patient acquisition. All authors have read and agreed to the published version of the manuscript.

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Competing interests None declared.

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