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Which physical therapy intervention is most effective in reducing secondary lymphoedema associated with breast cancer? Protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Lymphoedema associated with breast cancer is caused by an interruption of the lymphatic system, together with factors such as total mastectomy, axillary dissection, positive lymph nodes, radiotherapy, use of taxanes and obesity. Physiotherapy treatment consists of complex decongestive therapy, manual lymphatic drainage and exercises, among other interventions. Currently, there are several systematic review and randomised controlled trials that evaluate the efficacy of these interventions. However, at present, there are no studies that compare the effectiveness of all these physical therapy interventions. The purpose of this study is to determine which physical therapy treatment is most effective in reducing breast cancer-related lymphoedema, improving quality of life and reducing pain.

Methods and analysis MEDLINE, PEDro, CINAHL, EMBASE, LILACS and Cochrane Central Register of Controlled Trials will be searched for reports of randomised controlled trials published from database inception to June 2022. We will only include studies that are written in English, Spanish and Portuguese. We will also search grey literature, preprint servers and clinical trial registries. The primary outcomes are reduction of secondary lymphoedema associated with breast cancer, improvements in quality of life and pain reduction. The risk of bias of individual studies will be evaluated using the Cochrane Risk of Bias 2.0 Tool. A network meta-analysis will be performed using a random-effects model. First, pairs will be directly meta-analysed and indirect comparisons will be made between the different physical therapy treatments. The GRADE system will be used to assess the overall quality of the body of evidence associated with the main results.

Ethics and dissemination This protocol does not require approval from an ethics committee. The results will be disseminated via peer-reviewed publications.

PROSPERO registration number CDR42022323541.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study intends to evaluate the efficacy of all available physical therapy interventions in reducing breast cancer-related lymphoedema through a network meta-analysis.
⇒ This study will be carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.
⇒ The quality of the evidence will be evaluated using the GRADE approach.
⇒ A potential limitation of this study may be the heterogeneity between published studies due to the characteristics of the interventions.

INTRODUCTION

Breast cancer is a disease caused by abnormal and disorganised development of the epithelial cells in the breast ducts or lobes and is capable of spreading.[1 2] The WHO considers it one of the main public health problems in the world and the most recurring in women in developed and developing countries.[2] Medical treatments for breast cancer include (1) local treatments (partial mastectomy/conservative treatment, total mastectomy, axillary dissection and radiation therapy on the breast and adjacent ganglion chains) and (2) systemic treatments (chemotherapy, hormone therapy and monoclonal antibodies).[3] These treatments are not free of adverse consequences, which include anxiety, alterations in bone health, cardiotoxicity, peripheral neuropathy induced by chemotherapy, alterations in cognitive function, depressive symptoms, falling, fatigue, nausea, pain, diminished physical function, alterations in sexual function, trouble sleeping, intolerance of treatment and secondary lymphoedema associated with breast cancer, which affect the quality of life of those undergoing treatments.[4]

Secondary lymphoedema associated with breast cancer (BCRL) is considered one

of the most underestimated and debilitating complications of the disease's treatment.[5] The incidence varies in the general population, ranging between 3% and 65%, depending on the type of intervention received by the patient and the length of monitoring.[5–7] BCRL is caused by an interruption of the lymphatic system together with other factors,[5] such as total mastectomy, axillary dissection, positive lymph nodes, radiation therapy, use of taxanes and obesity.[5 7–10] Clinically, patients refer a heavy or rigid sensation in their limbs, limitations in movement, aches and pains in more severe cases, and present hardening and thickening of the skin or fibrosis.[11]

Physical therapy treatment (PTT)[12] focused on BCRL includes a wide range of interventions, such as complete decongestive therapy, manual lymphatic drainage, low-level laser therapy, shock waves, pneumatic pumps, Kinesio-taping, and endurance training/aerobic exercise, multimodal training, water training, yoga and Pilates. Currently, there are several systematic reviews that evaluate the efficacy of these different PTTs in reducing BCRL.[13–47]

Additionally, in 2020, the Academy of Oncologic Physical Therapy of the American Physical Therapy Association published a clinical practice guideline to aid in making informed decisions based on evidence from each one of the analysed physical therapy interventions through different randomised clinical studies (RCTs).[12] However, despite the large quantity of published evidence, there are currently no studies that compare the efficacy of these PTTs with each other, which makes it difficult to determine which treatment is most effective in reducing BCRL, improving quality of life and reducing pain.

In this context, network meta-analyses (NMA) emerge as a useful alternative as they include data from RCTs that do not necessarily present the same type of groups of comparison as a study network (indirect comparison). Based on this, an NMA allows direct and indirect comparisons between all physical therapy interventions, analysing their efficacy in reducing BCRL. It can also determine which intervention is the most effective and which has the greatest possibility of success compared with other interventions which have not been previously compared in RCTs.[48–50]

The purpose of this systematic review and network meta-analysis is to determine the comparative efficacy of the different physical therapy interventions in terms of reducing BCRL, improving quality of life, as well as reducing pain and incidence of adverse events.

METHODS AND ANALYSIS

This protocol was registered in PROSPERO (CDR42022323541) and was reported according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[51] (online supplementary appendix 1). The systematic review will be carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Any amendments to the protocol will be made through PROSPERO.

Eligibility criteria

Type of studies

Only RCTs will be included. We will only include studies that are written in English, Spanish and Portuguese.

Type of participants

We will include clinical trials on women with BCRL 15 years old and over.

Type of interventions

We will include studies where the intervention incorporates any of the following physical therapy interventions or any other reported in the included studies:

- Complete decongestive therapy.
- Manual lymphatic drainage.
- Low-level laser therapy.
- Pneumatic pumps.
- Kinesio-taping.
- High-intensity resistance exercise.
- Moderate-intensity resistance exercise.
- Low-intensity resistance exercise.
- Supervised resistance exercise.
- Unsupervised resistance exercise.
- Supervised endurance training.
- Unsupervised endurance training.
- Resistance exercise plus endurance training.
- Endurance training plus water endurance training.
- Resistance exercise plus endurance training plus stretching.
- Yoga.
- Pilates.
- Shock waves.
- Any combination of the above physical therapy interventions.

Type of comparisons

The different physical therapy interventions will be compared with each other and with their combinations, as well as with usual care, education or a group without physical therapy interventions.

Type of outcomes of interest

The outcomes will be on patients' condition.

Primary outcomes

- Reduction of secondary lymphoedema associated with breast cancer, measured by any of the following validated methods: volumetry of water movement, measurement of the limb's circumference, bioimpedance spectroscopy, dual X-ray absorptiometry and perometry.
- Improvements in quality of life, evaluated by any validated scale of generic or specific self-evaluation (eg, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ-BR23 questionnaires.

- Pain reduction, evaluated by any validated scale of generic or specific self-evaluation (eg, numeric rating scales (NRS) and visual analogue scale (VAS)).

All follow-ups reported by the primary studies will be considered.

Secondary outcomes

- Adverse events from the physical therapy intervention, such as increase in lymphoedema and pain.
- Range of motion, evaluated with goniometry or another validated method.
- Muscular strength, evaluated with dynamometry or another validated method.

Search strategies

The systematic database search will cover publications up to June 2022, with initial dates depending on database inception: from 1966 in MEDLINE, 1974 in EMBASE, 1982 in LILACS, 2008 in Cochrane Central Register of Controlled Trials, 1999 in PEDro and 1984 in CINAHL.

The details of the search strategy to be used in MEDLINE, PEDro, CINAHL, EMBASE, LILACS and Cochrane Central Register of Controlled Trials are described in online supplemental file 2. The search strategy used in MEDLINE was adapted so that it may be implemented in the remaining databases. Additionally, we will perform a search of the European grey literature database (http://www.opengrey.eu), examine the reference lists of all relevant articles, including studies and previous systematic reviews, and examine registers of RCTs (such as www.registroensayosclinicos.org, https://clinicaltrials.gov and https://www.who.int/clinical-trials-registry-platform), public access policies (https://publicaccess.nih.gov) and preprint servers (https://www.medrxiv.org, https://www.biorxiv.org).

Data management

All search results will be exported to Rayyan Intelligent Systematic Review (https://www.rayyan.ai).[52] Once duplicates have been eliminated, two researchers will independently screen by title and abstract and will review potential full text to be included. In case of discrepancy, a third researcher will make the final decision (CZ). A registry will be kept of the reasons for excluding studies.

Two researchers will independently extract data from the included studies to a standardised Excel spreadsheet. The spreadsheet will include the following sections: study identification, study design/setting, study population and participant demographics, baseline characteristics, details of the intervention and control conditions, outcome data of interest, and follow-up times.

Risk of bias of individual studies

Two authors of this review will independently evaluate the risk of bias of the included studies according to the Revised Cochrane Risk of Bias Tool (RoB 2.0).[53] In case of discrepancy, a third author will make the final decision (CZ).

RoB 2.0 evaluates the following domains: bias derived from the randomisation process, bias due to deviations from planned interventions, bias due to lack of results data, bias in the measurement of the result and bias in the selection of the reported results. A series of signalling questions will be included for each domain aiming to provide a structured approach to obtain relevant information on bias risk assessment. For each domain, the possible risk of bias judgements will be low risk of bias, some concerns and high risk of bias.[54] We will also present a summary of the 'risk of bias' graphically.

Missing data

If possible, the authors of the original studies will be contacted to obtain information on missing data and further details on any results of interest that could have been measured but were not formally reported in the study. We will not use any other statistical method to impute missing data.

Statistical analysis

Relative risk will be used for dichotomous results. As for continuous results, when the results of interest are measured with the same scales, the mean difference will be used with the corresponding 95% CI. The standardised mean difference will be calculated when the results of interest are measured with different scales.[53]

We will perform a meta-analysis during the previously established period of monitoring. First, we will meta-analyse in pairwise (direct) and will use a random-effects model for each comparison. A network diagram will then be generated and evaluated to determine the plausibility of an NMA. An NMA will be done using a frequentist analysis,[48 55] as this focus uses only the information obtained in the analysis, which is the statistical meaning's base, to evaluate a hypothesis from this study's data.[56]

Analyses will be done using Stata V.15 software.[57] We will use the Stata commands designed for NMA.[55 58 59] If the association is not adequate, the information will be described.

Heterogeneity analysis

We will use two methods to evaluate heterogeneity: the first will be an informal, visual inspection; the second will use the inconsistency test (I^2). However, the decision on heterogeneity will depend on the value presented by I^2, with greater than 50% indicating considerable heterogeneity.[53] In the pairwise meta-analysis, we will estimate the heterogeneity for each comparison. In the NMA, a common estimate for heterogeneity variance will be assumed in all physical therapy comparisons.

Transitivity analysis

As a concept, transitivity is based on the homogeneity between the studies included in the analysis.[48] Therefore, it allows evaluation of the singular characteristics of each study to conclude if the estimators generated by the statistical analysis are valid or not.[49] Transitivity refers to the assumption that should be adopted when an indirect

comparison is established via a common comparator (B is better than A and A is better than C, so it is assumed that B is better than C).[48 54 60 61] For example, patients included in studies that compare A versus a placebo should be similar in terms of population, intervention, comparison, results of interest and research design to those included in B versus placebo.[49] Within this context, we expect that the supposed transitivity will be maintained once it is assumed that the common treatment used to compare the different physical therapy interventions is similar in the different RCTs. The supposed transitivity will be evaluated by comparing the characteristics of the population, intervention, comparison, results of interest and research design of the different physical therapy interventions.

Inconsistency analysis

We will use the design-by-treatment model to evaluate inconsistency as it is the only model that can explain the different sources of inconsistency that may appear (*loop inconsistency*, *multiarm trial*, *design inconsistency*, *design-by-treatment interaction*).

We will use the node-splitting method to verify consistency between direct and indirect evidence.[48 62 63] Node-splitting corresponds to a more general but computationally intensive analysis, where the evidence is directly or indirectly divided from a particular comparison, or 'node', and can be applied to networks where trial data are available.[56]

Relative treatment classification

Once the compared efficacy for all the interventions has been evaluated, the results will be classified with a focus on the following[64]:

- Determining the order of the classification of the physical therapy interventions, using the surface under the cumulative ranking curve.
- Probability of being the best intervention.

Additional analysis

We expect to perform the following subgroup analysis based on the different monitoring periods and quality-of-life tools. We also plan to perform a sensitivity analysis to evaluate the impact of the trials' quality. Therefore, we consider a sensitivity analysis for each outcome by excluding studies that are at high risk of bias.

Reporting bias evaluation

Reporting bias will only be evaluated if at least 10 trials are included in the meta-analysis, as less than this number means that the test's statistical power is too low to distinguish the random from real asymmetry.[53] We will use Begg's test to analyse the funnel plot.[65 66] This method is based on the degree of association between the estimated effect size and its variations.[66] Therefore, a strong correlation represents reporting bias.[67]

If there is asymmetry, we will examine other causes besides reporting bias, such as selective outcome reporting, poor methodological quality in smaller studies and heterogeneity.

Concluding report

This systematic review will be reported according to the extension of the PRISMA guidance for systematic reviews that include network meta-analysis.[68]

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group focus to rate the efficacy estimations' certainty based on the NMA for all of the comparisons (direct and indirect) and all of the results of interest.[69] The certainty of evidence will be evaluated following the four steps proposed to evaluate the efficacy estimations' quality of the NMA's treatment[70]:

- Present the treatment's direct and indirect estimates for each comparison from the evidence network. The effect's direct estimate can be determined by a direct comparison (trial A vs trial B), and the indirect estimate by two or more direct comparisons that share a common comparator (eg, we infer the effects of A vs B from trial A vs trial C and from trial B vs trial C).
- Rate the quality of each direct and indirect effect estimate.
- Present the NMA estimate for each comparison in the evidence network.
- Rate the quality of each NMA effect estimate.

We will prepare a table that shows the 'summary of the network meta-analysis findings' according to the GRADE working group recommendations.[71] In order to evaluate the certainty of evidence, we will use the following domains[72]: risk of bias, inconsistency, indirect evidence, inaccuracy and reporting bias. Finally, the certainty of evidence will be classified as high, moderate, low or very low.[73]

Patient and public involvement

Patients and or public were not be involved in this study, either in planning or the design of the study. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

This protocol does not require approval from an ethics committee as it is a secondary study that compiles data from primary studies. The results will be disseminated via peer-reviewed publications.

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Contributors RAA-E, CZ, RG-A and PS contributed to the conception and design of the study. RAA-E developed the search strategies. RAA-E, CZ and PS designed the data analysis. All authors drafted the article and made the final approval of the version to be published.

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