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

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Abstract

Introduction: BCRL is produced by an interruption of the lymphatic system, together with factors such as total mastectomy, axillary dissection, positive lymph nodes, radiotherapy, the use of taxanes, and obesity. Physical therapy treatment (PPT) consists of the following interventions: CDT, MLD, LLLT, SW, NP, KT, ET, AT, MT, WT, Yoga, Pilates and a combination of these treatments. Currently, there are several SRs and RCTs that evaluate these interventions' efficacy. 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 at reducing BCRL, improving quality of life, and reducing pain.

Methods and analysis: The following databases will be systematically searched until june 2022: Medline, PEDro, CINHAL, EMBASE, Lilacs y CENTRAL.

We will include RCTs evaluating patients with BCRL whose intervention includes a PTT, which will be compared to customary care, without exercise/without treatment, education, other physical therapy interventions, or a combination of them. The main results will be the reduction BCRL, quality of life improvements, and pain reduction. Two researchers will independently examine the electronic search results and extract the information from the included studies. Two researchers will independently evaluate the risk of bias using the Cochrane tool (ROB 2). In the case of any discrepancy, a third researcher will make the decision.

A network meta-analysis will be performed using a random-effects model. First, pairs will be directly meta-analyzed, and indirect comparisons will be made between the different physical therapy treatments.

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.

Study's strengths and limitations

a) This study intends to be the first network meta-analysis to evaluate the efficacy of all physical therapy interventions available to reduce BCRL.
b) It will evaluate which physical therapy treatment is best at reducing BCRL, improving quality of life, and reducing pain.
c) The results of this network meta-analysis will provide evidence that will allow physicians to make the best-informed clinical decision based on the efficacy of the different treatments used by physical therapists for reducing BCRL.
d) The quality of the evidence will be evaluated by using the GRADE methodology.

Introduction

Breast cancer is a disease caused by abnormal and disorganized development of the epithelial cells in the breast ducts or lobes and is capable of spreading (1,2). The World Health Organization (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 used for breast cancer include: a) Local treatments (Partial mastectomy/conservative treatment; Total mastectomy; Axillary dissection and radiation therapy on the breast and adjacent ganglion chains) and b) 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 of cognitive function, depressive symptoms, falling, fatigue, nausea, pain, diminished physical function, alterations in sexual function, trouble sleeping, intolerance of treatment and secondary lymphedema associated with breast cancer, which affect the quality of life of those undergoing these treatments (4).

Secondary lymphedema associated with breast cancer (BCRL) is considered one of the most underestimated and debilitating complications of the disease's treatment (5). Incidence varies in the general population, presenting a range between 3% and 65%, which will depend on the type of intervention received by the patient and the length of monitoring (5–7). BCRL is produced by an interruption of the lymphatic system together with other factors(5), such as total mastectomy (TM), axillary dissection (AD), positive lymph nodes (PLN), radiation therapy (RT), use of taxanes (UT) and obesity (OB)(5,7–10).

Clinically, patients refer to a heavy or rigid sensation in their limbs, limitation of movement, aches and pains in more severe cases, and present hardening and thickening of the skin or fibrosis (14).

Physical therapy treatment (PTT) (15) focused on BCRL include a wide range of interventions, such as Complete Decongestive Therapy (CDT), Manual Lymphatic Drainage (MLD); low-level laser therapy (LLLT), shockwaves (SW), pneumatic

pumps (NP); Kinesio-taping (KT); endurance training (ET), aerobic training (AT), multimodal training (MT), water training (WT), Yoga and Pilates.

Currently, there are several systematic reviews that evaluate the efficacy of these different PPT in the reduction of BCRL (16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27)(28)(29)(30)(31)(32)(33)(34)(35)(36)(37)(38)(39)(40)(41)(42)(43)(44)(45)(46)(47)(48)(49)(50)(51).

Additionally, in 2020, the Academy of Oncologic Physical Therapy of the American Physical Therapy Association (APTA) published a clinical practice guideline to aid in making informed decisions based on evidence for each one of the analyzed physical therapy interventions through different randomized clinical studies (RCTs) (15). However, despite the large quantity of published evidence, there are currently no studies that compare the efficacy of these PTT with each other, which makes it difficult determining which treatment is most effective at 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 for making direct and indirect comparisons between all the physical therapy interventions, analyzing their efficacy in reducing BCRL. They can also determine which intervention is the most effective and which has the greatest possibility of success compared with the other interventions, which have not been previously compared in the RCTs (52–54).

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 reduction of BCRL improving quality of life, as well as reducing pain and incidence of adverse events.

Method and analysis

This protocol was registered in PROSPERO and was elaborated according to the guidelines in the Preferred Report Elements for Systematic Reviews and Meta-analysis Protocols (PRISMA-P)(55).

Patient and public participation

Patients and/or the public will not be involved in this study, neither in its planning nor design. Patients will not be invited to comment on the study design and will not be consulted on developing patient-relevant outcomes or interpreting the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

Eligibility criteria

Type of studies

Only randomized clinical trials will be included.

We will only include studies that are written in English and Spanish

Type of participants

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

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:

1. Complete Decongestive Therapy.
2. Manual Lymphatic Drainage.
3. Low-level laser therapy.
4. Pneumatic pumps.
5. Kinesio-taping.
6. High intensity endurance training.
7. Moderate intensity endurance training.
8. Low intensity endurance training.
9. Supervised endurance training.
10. Unsupervised endurance training.
11. Supervised aerobic training.
12. Unsupervised aerobic training.
13. Endurance training plus aerobic training.
14. Endurance training plus water aerobics training.
15. Endurance training + aerobic training + stretching.
16. Yoga.
17. Pilates.
18. Shock waves.
19. Any combination of these physical therapy interventions (#1 – #18).

The different physical therapy interventions will be compared to each other, with a combination of them, usual care, education, or with a group without physical therapy interventions.

Outcomes of interest
The outcomes will be for the patients' condition.

Primary outcomes
-Reduction of secondary lymphedema 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 (DXA) and perometry.
-Improvements in quality of life, evaluated by any validated scale of generic or specific self-evaluation (for example EORTC-QLQ-C30).
-Pain reduction, evaluated by any validated scale of generic or specific self-evaluation (for example NSR and VAS).

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

Secondary outcomes
-Adverse events from the physical therapy interventions such as an increase in lymphedema and pain.
- Range of motion (ROM), evaluated with goniometry or another validated method.
-Muscular strength, evaluated with dynamometry or another validated method.

Search strategies
A systematic search of the following databases will be conducted: Medline, PEDro, CINHAL, EMBASE, Lilacs y Cochrane Central Register of Controlled Trials. There will be no language restriction. The details of the search strategy to be used in Medline is described in Appendix 1:

The search strategy used in Medline will be 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, previous systematic revisions, and registers of RCTs, such as Clinical trial registry (www.registroensayosclinicos.org), Public access policies (https://publicaccess.nih.gov), clinical trials (https://clinicaltrials.gov), International Clinical Trial Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform), MesRxiv (https://www.medrxiv.org), BioRxiv (https://www.biorxiv.org).

Data management
All search results will be exported to Rayyan INTELLIGENT SYSTEMATIC REVIEW (https://www.rayyan.ai)(56). Once duplicates have been eliminated, two researchers will independently screen by title and abstract and then 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 studies being excluded.

Two researchers will independently extract data from the included studies to a standardized 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, follow-up times.

Risk of bias in individual studies

Two of this review's authors will independently evaluate the risk of bias for the included studies, according to the Revised Cochrane Risk of Bias Tool (RoB 2.0) (57). In the case of discrepancy, a third author will make the final decision (CZ).

ROB 2 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 result. A series of signaling questions will be included for each domain that aims to provide a structured approach to obtain relevant information on bias risk assessment. For each domain, the possible risk of bias judgments will be: low risk of bias, some concerns, and high risk of bias (60). We will also present a summary of the 'risk of bias' graphically.

Regarding missing data

If possible, the authors of the original studies will be contacted to obtain information on the 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 (RR) will be used for the dichotomous results. As for continuous results, when the results of interest are measured with the same scales, the mean differences (MD) will be used with their corresponding confidence intervals at 95% (CI). The standardized mean differences (SMD) will be calculated when the results of interest are measured with different scales (57).

We will perform a meta-analysis during the previously established period of monitoring. First, we will meta-analyze in pairwise (direct) and we will use the random effects model for each comparison. Then, the network diagram will be generated and evaluated to determine the plausibility of a network meta-analysis. Network meta-analysis will be done using a frequentist analysis (52,62), 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 (63).

The analyses will be done using Stata, Version 15 software (StataCorp, College Station, Texas, E.E.U.U)(64). We will use the Stata commands designed for network meta-analysis (62,65,66). 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 (57). In the pairwise meta-analysis, we will estimate heterogeneity for each comparison.
In the network meta-analysis, a common estimate for heterogeneity variance will be assumed in all the physical therapy comparisons.

Transitivity analysis
As a concept, transitivity is based on the homogeneity between the studies included in the analysis (52). Therefore, it allows for evaluating the singular characteristics of each study to conclude if the estimators generated by the statistical analysis are valid or not.(53) 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)(52,67–69). For example, patients that are included in studies that compare A versus a placebo should be similar in terms of: population; intervention; comparison; result of interest and research design, to those that are included in B versus placebo(53). 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 randomized clinical trials.
The supposed transitivity will be evaluated by comparing the characteristics of 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, multi-arm trial, design inconsistency, design-by-treatment interaction)*.
We will use the node-splitting method to verify consistency between the direct and indirect evidence (52,70,71). 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 is available (63).

Relative treatment classification
Once the compared efficacy for all of the interventions is evaluated, the results will be classified with a focus on (72):

1) Determining the order of the classification of the physical therapy interventions, using the surface under the cumulative ranking curve (SUCRA).
2) Probability of being the best intervention.

Additional analysis
We expect to perform the following subgroup analysis based on the different monitoring periods and the 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(57). We will use Begg's test to analyze the funnel plot (73,74). This method is based on the degree of association between the estimated effect size and its variations (74). Therefore, a strong correlation represents reporting bias (75).

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

The systematic revision will take place and will be reported according to the extension of the PRISMA declaration for systematic revisions that include network meta-analysis (PRISMA-NMA)(76).

We will use the GRADE working group focus to rate the efficacy estimations' certainty based on the network meta-analysis for all of the comparisons (direct and indirect) and all of the results of interest (77). The evidence's certainty will be evaluated following the four steps proposed to evaluate the efficacy estimations' quality of the network meta-analysis's treatment (78):

1. 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 (trail A versus trial B), and the indirect estimate by two or more direct comparisons that share a common comparer (for example: we infer the effects of A versus B from the trial A versus trial C and from trial B versus trial C).
2. Rate the quality of each direct and indirect effect estimate.
3. Present the network meta-analysis estimate for each comparison in the evidence network.
4. Rate the quality of each network meta-analysis effect estimate.

We will prepare a table that shows the "summary of the network menta-analysis findings" according to the GRADE working group recommendations (79).

In order to evaluate the evidence's certainty, we will use the following domains (80): Risk of bias, Inconsistency, Indirect evidence, Inaccuracy, Reporting bias.

Finally, the certainty of evidence will be classified as: high moderate, low or very low(81).

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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Patient consent for publication: Not required

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Appendix 1: Search strategy used on Medline.

1# "Breast Cancer Lymphedema"
2# "Breast Cancer Lymphedema"[Mesh]
3# Breast Cancer Treatment-Related Lymphedema
4# or/ 1-3
5# Low-Level Light Therapy"[Mesh]
6# "Low-Level Light Therapy"
7# LLLT
8# Intermittent Pneumatic Compression Pump
9# Pneumatic Compression Pump
10# "Manual Lymphatic Drainage"[Mesh]
11# "Manual Lymphatic Drainage"
12# Pneumatic compression
13# Complex Decongestive Therapy
14# Kinesiotaping
15# Kinesio taping
16# Linfotaping
17# "Yoga"[Mesh]
18# "Yoga"
19# "Exercise Movement Techniques"[Mesh]
20# Pilates Training
21# "Extracorporeal Shockwave Therapy"[Mesh]
22# "Extracorporeal Shockwave Therapy"
23# "Exercise Therapy"[Mesh]
24# "Exercise Therapy"
25# "Resistance Training"[Mesh]
26# "Resistance Training"
27# Strength Training
28# Weight Lifting Exercise Program
29# Weight lifting exercise
30# Aerobic training
31# Endurance training
32# Aquatic Therapy
33# or/5-32
34# and/4,33

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

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Abstract

Introduction: Lymphedema associated with breast cancer is produced by an interruption of the lymphatic system, together with factors such as total mastectomy, axillary dissection, positive lymph nodes, radiotherapy, the use of taxanes, and obesity. Physiotherapy treatment consists of complex decongestive therapy, manual lymphatic drainage, exercises, among other interventions. Currently, there are several systematic review and randomized controlled trials that evaluate these interventions' efficacy. 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 at reducing BCRL, improving quality of life, and reducing pain.

Methods and analysis: Medline, PEDro, CINHAL, EMBASE, Lilacs and Cochrane Central Register of Controlled Trials will be searched for reports of randomized 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 lymphedema associated with breast cancer, improvements in quality of life and pain reduction. The risk of bias for individual studies will be evaluate using the Cochrane tool (ROB 2). A network meta-analysis will be performed using a random-effects model. First, pairs will be directly meta-analyzed, and indirect comparisons will be made between the different physical therapy treatments. 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.

Study registration number: PROSPERO, CDR42022323541.

Strengths and limitations of this study

* This study intends will evaluate the efficacy of all physical therapy interventions available to reduce BCRL through a network meta-analysis.
* The study will be carried out according to the recommendation of Cochrane handbook for systematic reviews of interventions.
* The quality of the evidence will be evaluated by using the GRADE approach.
* A potential limitation of this study may be the heterogeneity between published studies due to characteristics of interventions.

Introduction

Breast cancer is a disease caused by abnormal and disorganized development of the epithelial cells in the breast ducts or lobes and is capable of spreading (1,2). The World Health Organization (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 used for breast cancer include: a) Local treatments (Partial mastectomy/conservative treatment; Total mastectomy; Axillary dissection and radiation therapy on the breast and adjacent ganglion chains) and b) 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 of cognitive function, depressive symptoms, falling, fatigue, nausea, pain, diminished physical function, alterations in sexual function, trouble sleeping, intolerance of treatment and secondary lymphedema associated with breast cancer, which affect the quality of life of those undergoing these treatments (4).

Secondary lymphedema associated with breast cancer (BCRL) is considered one of the most underestimated and debilitating complications of the disease's treatment (5). Incidence varies in the general population, presenting a range between 3% and 65%, which will depend on the type of intervention received by the patient and the length of monitoring (5–7). BCRL is produced 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 to a heavy or rigid sensation in their limbs, limitation of 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 include a wide range of interventions, such as Complete Decongestive Therapy, Manual Lymphatic Drainage, low-level laser therapy, shockwaves, pneumatic pumps, Kinesio-taping; endurance training/aerobic exercise, multimodal training, water training, Yoga and Pilates.

Currently, there are several systematic reviews that evaluate the efficacy of these different PPT in the reduction of BCRL

(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27)(28)(29)(30)(31)(32)(33) (34)(35)(36)(37)(38)(39)(40)(41)(42)(43)(44)(45)(46)(47)(48).

Additionally, in 2020, the Academy of Oncologic Physical Therapy of the American Physical Therapy Association (APTA) published a clinical practice guideline to aid in making informed decisions based on evidence for each one of the analyzed physical therapy interventions through different randomized clinical studies (RCTs) (12). However, despite the large quantity of published evidence, there are currently no studies that compare the efficacy of these PTT with each other, which makes it difficult determining which treatment is most effective at 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 for making direct and indirect comparisons between all the physical therapy interventions, analyzing their efficacy in reducing BCRL. They can also determine which intervention is the most effective and which has the greatest possibility of success compared with the other interventions, which have not been previously compared in the RCTs (49–51).

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 reduction of BCRL improving quality of life, as well as reducing pain and incidence of adverse events.

Method and analysis

This protocol was registered in PROSPERO (CDR42022323541) and was elaborated according to the guidelines in the Preferred Report Elements for Systematic Reviews and Meta-analysis Protocols (PRISMA-P)(52) (online supplementary appendix 1) The systematic review will be carried out according to the recommendation of Cochrane handbook for systematic reviews of interventions. Any amendments to the protocol will be made through PROSPERO.

Eligibility criteria

Type of studies

Only randomized clinical trials will be included.

We will only include studies that are written in English, Spanish and Portuguese.

Type of participants

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

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:

1. Complete Decongestive Therapy.
2. Manual Lymphatic Drainage.
3. Low-level laser therapy.
4. Pneumatic pumps.
5. Kinesio-taping.
6. High intensity resistance exercise.
7. Moderate intensity resistance exercise.
8. Low intensity resistance exercise.
9. Supervised resistance exercise.
10. Unsupervised resistance exercise.
11. Supervised endurance training.
12. Unsupervised endurance training.
13. Resistance exercise plus endurance training.
14. Endurance training plus water endurance training.
15. Resistance exercise + endurance training + stretching.
16. Yoga.
17. Pilates.
18. Shock waves.
19. Any combination of these physical therapy interventions (#1 – #18).

Type of comparations

The different physical therapy interventions will be compared to each other, with a combination of them, usual care, education, or with a group without physical therapy interventions.

Type of outcomes of interest

The outcomes will be for the patients' condition.

Primary outcomes
-Reduction of secondary lymphedema 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 (DXA) and perometry.
-Improvements in quality of life, evaluated by any validated scale of generic or specific self-evaluation (for example EORTC-QLQ-C30).
-Pain reduction, evaluated by any validated scale of generic or specific self-evaluation (for example NSR and VAS).

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

Secondary outcomes
-Adverse events from the physical therapy interventions such as an increase in lymphedema and pain.
- Range of motion (ROM), 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 CENTRAL, 1999 in PEDro and 1984 in CINHAL. We will only include studies that are written in English, Spanish and Portuguese.
The details of the search strategy to be used in Medline, PEDro, CINHAL, EMBASE, Lilacs and Cochrane Central Register of Controlled Trials are described in Appendix 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)(53). Once duplicates have been eliminated, two researchers will independently screen by title and abstract and then 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 studies being excluded.
Two researchers will independently extract data from the included studies to a standardized 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, follow-up times.

Risk of bias in individual studies

Two of this review's authors will independently evaluate the risk of bias for the included studies, according to the Revised Cochrane Risk of Bias Tool (RoB 2.0) (54). In the case of discrepancy, a third author will make the final decision (CZ).

ROB 2 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 result. A series of signaling questions will be included for each domain that aims to provide a structured approach to obtain relevant information on bias risk assessment. For each domain, the possible risk of bias judgments will be: low risk of bias, some concerns, and high risk of bias (60). We will also present a summary of the 'risk of bias' graphically.

Regarding missing data

If possible, the authors of the original studies will be contacted to obtain information on the 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 (RR) will be used for the dichotomous results. As for continuous results, when the results of interest are measured with the same scales, the mean differences (MD) will be used with their corresponding confidence intervals at 95% (CI). The standardized mean differences (SMD) will be calculated when the results of interest are measured with different scales (54).

We will perform a meta-analysis during the previously established period of monitoring. First, we will meta-analyze in pairwise (direct) and we will use the random effects model for each comparison. Then, the network diagram will be generated and evaluated to determine the plausibility of a network meta-analysis. Network meta-analysis will be done using a frequentist analysis (49,55), 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).

The analyses will be done using Stata, Version 15 software (StataCorp, College Station, Texas, E.E.U.U)(57). We will use the Stata commands designed for network meta-analysis (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 (54). In the pairwise meta-analysis, we will estimate heterogeneity for each comparison.

In the network meta-analysis, a common estimate for heterogeneity variance will be assumed in all the physical therapy comparisons.

Transitivity analysis

As a concept, transitivity is based on the homogeneity between the studies included in the analysis (49). Therefore, it allows for evaluating the singular characteristics of each study to conclude if the estimators generated by the statistical analysis are valid or not.(50) 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)(49,60–62). For example, patients that are included in studies that compare A versus a placebo should be similar in terms of: population; intervention; comparison; result of interest and research design, to those that are included in B versus placebo(50). 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 randomized clinical trials.

The supposed transitivity will be evaluated by comparing the characteristics of 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, multi-arm trial, design inconsistency, design-by-treatment interaction)*.

We will use the node-splitting method to verify consistency between the direct and indirect evidence (49,63,64). 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 is available (56).

Relative treatment classification

Once the compared efficacy for all of the interventions is evaluated, the results will be classified with a focus on (65):

1) Determining the order of the classification of the physical therapy interventions, using the surface under the cumulative ranking curve (SUCRA).
2) Probability of being the best intervention.

Additional analysis

We expect to perform the following subgroup analysis based on the different monitoring periods and the 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(54). We will use Begg's test to analyze the funnel plot (66,67). This method is based on the degree of association between the estimated effect size and its variations (67). Therefore, a strong correlation represents reporting bias (68).
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
The systematic reviews will be reported according to the extension of the PRISMA guidance for systematic reviews that include network meta-analysis (PRISMA-NMA)(69).
We will use the GRADE working group focus to rate the efficacy estimations' certainty based on the network meta-analysis for all of the comparisons (direct and indirect) and all of the results of interest (70). The evidence's certainty will be evaluated following the four steps proposed to evaluate the efficacy estimations' quality of the network meta-analysis's treatment (71):

1. 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 (trail A versus trial B), and the indirect estimate by two or more direct comparisons that share a common comparer (for example: we infer the effects of A versus B from the trial A versus trial C and from trial B versus trial C).
2. Rate the quality of each direct and indirect effect estimate.
3. Present the network meta-analysis estimate for each comparison in the evidence network.
4. Rate the quality of each network meta-analysis effect estimate.

We will prepare a table that shows the "summary of the network menta-analysis findings" according to the GRADE working group recommendations (72).

In order to evaluate the evidence's certainty, we will use the following domains (73): Risk of bias, Inconsistency, Indirect evidence, Inaccuracy, Reporting bias.

Finally, the certainty of evidence will be classified as: high moderate, low or very low(74).

Patient and public involvement
None.

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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Appendix 1: PRISMA-P Checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line Number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title:					
Identification	1a	Identify the report as a protocol of a systematic review	X		1 - 3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	X		79
Authors:					
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		6 - 42
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		302 - 395
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	N/A
Support:					
Sources	5a	Indicate sources of financial or other support for the review	X		396 - 397
Sponsor	5b	Provide name for the review funder and/or sponsor	X		396 - 397
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		396 - 397
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		127 - 151
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		152 - 155
METHODS					
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	X		168 - 225
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	X		227 - 242
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits,	X		Appendix A

		such that it could be repeated			
Study records:					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		243 - 254
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	X		243 - 254
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		243 - 254
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	X		250 - 254
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		206 - 255
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		256 - 267
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	X		
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	X		276 -336
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	X		338 - 343
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		269 - 292
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	X		346 - 355
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	X		361 - 384

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Appendix 2: Search strategy used on Medline.

1 "Breast Cancer Lymphedema"[Mesh]
2 "Breast Cancer Lymphedema"
3 Breast Cancer Treatment-Related Lymphedema
4 or/1-3
5 "Low-Level Light Therapy"[Mesh])
6 "Low-Level Light Therapy"
7 LLLT
8 "Manual Lymphatic Drainage"[Mesh]
9 "Manual Lymphatic Drainage"
10 Intermittent Pneumatic Compression Pump
11 pneumatic compression pump
12 pneumatic compression
13 Complete Decongestive Therapy
14 Complex Decongestive Therapy
15 "Athletic Tape"[Mesh]
16 "Athletic Tape"
17 Kinesio taping
18 linfotaping
19 "Yoga"[Mesh]
20 "Yoga"
21 "Exercise Movement Techniques"[Mesh]
22 Pilates Training
23 "Extracorporeal Shockwave Therapy"[Mesh]
24 "Extracorporeal Shockwave Therapy"
25 "Exercise Therapy"[Mesh]
26 "Exercise Therapy"
27 "Resistance Training"[Mesh]
28 "Resistance Training"
29 strength training
30 Weigth Lifting Excercise Program
31 Weigth Lifting Exercise Program
32 weight lifting exercise
33 Weigth Lifting Exercise
34 aerobic training
35 endurance training
36 "Aquatic Therapy"[Mesh]
37 "Aquatic Therapy"
38 or/5-37
39 clinical[Title/Abstract]
40 trial[Title/Abstract]
41 clinical trials as topic[MeSH Terms]

42 clinical trial[Publication Type]
43 random*[Title/Abstract]
44 random allocation[MeSH Terms]
45 therapeutic use[MeSH Subheading]
46 or/39-45
47 and/4,38, 46

Search strategy used on Lilacs:

1 linfedema del cáncer de mama
2 linfedema posmastectomía
3 linfedema relacionado con el tratamiento del cáncer de mama
4 or/1-3
5 terapia por luz de baja intensidad
6 bioestimulación por láser
7 lllt
8 drenaje línfático manual
9 masaje de drenaje linfático
10 aparatos de compresión neumática intermitente
11 media de compresión neumática
12 terapia descongestiva completa
13 cinta atlética
14 kinesio tape
15 vendaje neuromuscular
16 técnicas de ejercicio con movimiento
17 método pilates
18 ejercicio físico
19 terapia por ejercicio
20 tratamiento con ondas de choque extracorpóreas
21 tratamiento con ondas de choque
22 entrenamiento de fuerza
23 programa de fortalecimiento levantando peso
24 musculación
25 entrenamiento aeróbico
26 entrenamiento de resistencia
27 (balneoterapia)
28 or/5-26
29 and/4,28
30 Filtro: type_of_study:("clinical_trials")

Search strategy used on Medline CINHAL:

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 "Complete Decongestive Therapy"
6 "Manual Lymphatic Drainage"
7 "Low-level laser therapy"
8 "Low-level light therapy"
9 "Pneumatic pumps"
10 "Pneumatic compression pumps"
11 Kinesio-taping
12 linfotaping
13 "High intensity endurance training"
14 "Moderate intensity endurance training"
15 "Low intensity endurance training"
16 "Supervised endurance training"
17 "Unsupervised endurance training"
18 "Supervised aerobic training"
19 "Unsupervised aerobic training"
20 “Weight lifting exercise”
21 pilates
22 yoga
23 “Exercise Movement Techniques”
24 "shock waves"
25 "High-Energy shock waves"
26"Endurance training"
27 "aerobic training"
28 "Endurance training"
29 "water aerobics training"
30"Endurance training"
31 "aerobic training"
32 Stretching
33 or/5-32
34 “randomized clinical trial”
35 and/4,33,34

Search strategy used on Embase:

1 'breast cancer lymphedema'/exp
2 'breast cancer treatment-related lymphedema'
3 or/1,2
4 'low-level light therapy'/exp
5 lllt:ab,ti
6 'manual lymphatic drainage'/exp
7 'intermittent pneumatic compression pump'
8 'complete decongestive therapy'/exp
9 'athletic tape'/exp
10 'kinesio taping'/exp
11 linfotaping
12 'yoga'/exp
13 'exercise movement techniques'/exp
14 'pilates training'
15 'extracorporeal shockwave therapy'/exp
16 'resistance training'/exp
17 'weight lifting exercise'/exp
18 'aerobic training'/exp
19 'endurance training'/exp
20 'exercise therapy'/exp
21 'aquatic therapy'/exp
22 OR/4-21
23 and/3,22
24 Filter: [randomized controlled trial]/lim

Search strategy used on PEDro:

Advanced Search:

Abstract & Title: 'breast cancer lymphedema'
Therapy: -
Problem: -
Body Part: upper arm, shoulder or shoulder girdle
Subdiscipline: -
Topic: -
Method: clinical trial
Autor/Association: -
Title Only: -
Source: -
Published Since: -
New records added since: -
Score at least: -
When Searching: Match all serch term (AND)

Search strategy used on CENTRAL:

Search #1

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 "Pneumatic pumps" OR "Pneumatic compression pumps"
6 "Low-level light therapy"
7 "Low-level laser therapy"
8 "Complete Decongestive Therapy"
9 "Manual Lymphatic Drainage"
10 or/5-9
11 randomized clinical trial
12 and/4,10,11

Search #2

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 Kinesio-taping
6 linfotaping
7 “Weight lifting”
8 or/5-7
9 randomized clinical trial
10 and/4,8,9

Search #3

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 "High intensity endurance training"
6 "Moderate intensity endurance training"
7 "Low intensity endurance training"
8 "Supervised endurance training"
9 "Unsupervised endurance training"
10 "Supervised aerobic training"
11 "Unsupervised aerobic training"
12 or/5-11
13 randomized clinical trial

14 and/4,12,13

Search #4

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 pilates
6 yoga
7 "shock waves"
8 "High-Energy shock waves"
9 “Exercise Movement Techniques”
10 or/5-9
11 randomized clinical trial
12 and/4,10,11

Search #5

1 "breast cancer lymphedema"
2 "breast cancer-related lymphedema"
3 "Breast Cancer Treatment-Related Lymphedema"
4 or/1-3
5 "Endurance training"
6 "aerobic training"
7 "water aerobics training"
8 stretching
9 and/5,6
10 and/5,7
11 and/5,6,8
12 or/9,10,11
13 randomized clinical trial
14 and/12,13