INPLASY

EFFECTIVENESS OF MANUAL LYMPHATIC DRAINAGE AND INTERMITTENT PNEUMATIC COMPRESSION ON THE REDUCTION OF UPPER EXTREMITY LYMPHEDEMA SECONDARY TO BREAST CANCER: A SYSTEMATIC REVIEW

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INTRODUCTION

Review question / Objective Review question: In women with upper-extremity lymphedema secondary to breast cancer treatment, what are the effects of manual lymphatic drainage (MLD) and/or intermittent pneumatic compression (IPC), applied alone or in combination with other conservative treatments, compared with other conservative interventions or the same background treatment without the modality of interest, on upper-extremity lymphedema volume and/or circumference?

Objective: This systematic review aimed to synthesize evidence from randomized controlled trials on the effectiveness of MLD and IPC, applied alone or as adjuncts to conservative treatment, in reducing the volume and/or circumference of breast cancer-related upper-extremity lymphedema. Where reported, the review also assessed whether adding MLD or IPC provided an additional benefit over the comparator intervention.

Rationale Breast cancer-related lymphedema (BCRL) is a chronic complication of breast cancer treatment that can cause persistent upper-limb swelling, pain, heaviness, reduced mobility, functional limitations, and deterioration in quality of life. Conservative management remains the principal therapeutic approach. Manual lymphatic drainage (MLD) and intermittent pneumatic compression (IPC) are frequently used either as individual modalities or as components of multimodal interventions such as complex decongestive therapy.

However, considerable variability exists among treatment protocols. MLD may be delivered alone or combined with compression, exercise, skin care, and self-management strategies, while IPC protocols differ in pressure, application time, treatment frequency, device characteristics, and accompanying therapies. Differences in comparators, intervention dosage, outcome definitions, measurement methods, and assessment time points further complicate interpretation of the available evidence.

Consequently, it remains uncertain whether observed reductions in lymphedema are attributable to MLD or IPC themselves, to the other components of multimodal treatment, or to their combined effects.

This systematic review was therefore undertaken to synthesize evidence from randomized controlled trials and determine the effectiveness of MLD and IPC, applied alone or as adjuncts to conservative treatment, in reducing the volume and/or circumference of upper-extremity lymphedema secondary to breast cancer treatment. It also sought to establish whether adding either modality provided additional benefit over the comparator treatment.

Condition being studied Breast cancer-related lymphedema is a form of secondary lymphedema caused by damage to or disruption of the lymphatic system following breast cancer treatment, including breast surgery, sentinel lymph node biopsy, axillary lymph node dissection, and radiotherapy. Impaired lymphatic transport leads to the accumulation of protein-rich interstitial fluid in the affected upper extremity, producing increased limb volume or circumference and, in some cases, progressive tissue fibrosis.

The condition may develop within months of treatment or appear several years later. Common manifestations include swelling, heaviness, pain, numbness, weakness, reduced joint mobility, and limitations in upper-limb function and daily activities. Because no definitive curative treatment is currently available, management focuses on reducing edema, controlling symptoms, preserving function, and preventing progression. This review specifically addressed women diagnosed with upper-extremity lymphedema secondary to breast cancer treatment.

METHODS

Search strategy An electronic literature search was conducted in PubMed, Scopus, Web of Science Core Collection, and CINAHL in November 2023. Controlled vocabulary, including MeSH terms and CINAHL Headings, and free-text terms were combined to represent three concepts: breast cancer, upper-extremity lymphedema, and the conservative interventions of interest. Search terms included "breast cancer lymphedema," "breast neoplasms," "lymphedema," "lymphoedema," "manual lymphatic drainage," "manual lymph drainage," "intermittent pneumatic compression," "complex decongestive therapy," "complete decongestive therapy," and "decongestive lymphatic therapy." Synonyms within each concept were combined using OR, and the main concepts were combined using AND.

Database-specific search fields were used: MeSH and title/abstract in PubMed; title, abstract, and keywords in Scopus; Topic in Web of Science; and CINAHL Headings, title, and abstract in CINAHL. Searches were restricted to publications from 1 January 2013 to 30 November 2023 and to studies published in English, Spanish, or Portuguese. Clinical trial, controlled clinical trial, randomized controlled trial, or clinical study filters and related terms were applied according to the functions available in each database. The searches retrieved 234 records: PubMed (n = 39), Scopus (n = 50), Web of Science (n = 133), and CINAHL (n = 12). The complete database-specific search strategies are reported in Supplementary Table 1.

Participant or population The population comprised women diagnosed with upper-extremity lymphedema secondary to breast cancer treatment, including breast surgery, mastectomy, lymph node procedures, radiotherapy, or other related oncological treatments. Eligible participants had established lymphedema affecting the arm or upper extremity on the treated side. Studies involving participants without diagnosed lymphedema, interventions aimed exclusively at preventing lymphedema, primary lymphedema, or secondary lymphedema unrelated to breast cancer treatment were not eligible.

Intervention The interventions of interest were manual lymphatic drainage (MLD) and intermittent pneumatic compression (IPC) for the treatment of breast cancer-related upper-extremity lymphedema. Eligible interventions included MLD alone or combined with standard conservative treatment; IPC alone or combined with standard conservative treatment; and MLD plus IPC, either alone or as components of a multimodal treatment. Co-interventions could include compression bandaging or garments, therapeutic exercise, skin care, education, and self-management strategies. All techniques, devices, pressures, session durations, treatment frequencies, and intervention periods meeting these definitions were considered.

Comparator Comparators consisted of another active conservative intervention or the same background treatment without the therapeutic modality being evaluated. Eligible comparisons included complete decongestive therapy without MLD when assessing the additional effect of MLD; MLD or complete decongestive therapy without IPC when assessing the additional effect of IPC;

and compression garments or other standard conservative treatments. The comparator had to be administered concurrently to a control group.

Study designs to be included Randomized controlled clinical trials comparing MLD and/or IPC, applied alone or with other conservative treatments, against a concurrent control intervention were included. Parallel-group and randomized crossover trials were eligible, provided that treatment allocation was randomized and the results for each intervention condition were reported separately. Non-randomized and observational studies were excluded.

Eligibility criteria Additional eligibility criteria were publication between 1 January 2013 and 30 November 2023, publication in English, Spanish, or Portuguese, availability of the full-text report, and sufficient quantitative information to interpret the primary outcome, including the measurement method and unit. Studies were excluded when the full text was unavailable, random allocation was absent or could not be verified, the intervention was performed exclusively through patient self-administration, or upper-extremity volume or circumference was not reported in an interpretable unit. When multiple reports described the same trial, they were treated as a single study.

Information sources The electronic information sources were PubMed, Scopus, Web of Science Core Collection, and CINAHL. The final searches were conducted in November 2023 and covered publications from January 2013 to November 2023. Database-specific controlled vocabulary and free-text terms were used, as described in the search strategy section. No searches of grey literature sources or clinical trial registries were conducted.

Main outcome(s) The primary outcome was the change in upper-extremity lymphedema from baseline to the primary post-intervention assessment, measured through affected-limb volume and/or circumference. Volume outcomes included absolute limb volume, excess volume relative to the unaffected limb, and percentage volume reduction, measured by direct volumetry or calculated from serial circumference measurements and expressed in millilitres (mL). Circumference was measured with a tape at predefined anatomical locations and expressed in centimetres (cm).

The primary assessment corresponded to the end-of-treatment measurement reported by each trial, generally after approximately three to four weeks of intervention. Longer-term follow-up measurements were recorded when available. Extracted effect measures included baseline and post-intervention means, within-group change, between-group differences in change, percentage reduction, and measures of statistical uncertainty when reported. Interpretation prioritised between-group comparisons.

Additional outcome(s) When reported by the included trials, additional outcomes were extracted descriptively. These included subjective symptoms associated with lymphedema, such as heaviness, tension, pain, and discomfort; dermal or tissue thickness assessed by ultrasonography; upper-limb function, including grip strength; and health-related quality of life measured using study-specific questionnaires. Outcomes were recorded at the end of treatment and at subsequent follow-up assessments when available. Extracted measures included baseline and post-intervention values, within-group changes, and between-group differences. These outcomes were not required for study eligibility and were synthesised narratively because of differences in measurement instruments, definitions, and assessment time points.

Data management Search records were exported and collated in an electronic database using Microsoft Excel. Duplicate records were identified and removed before screening. Two reviewers independently screened titles and abstracts, assessed potentially eligible full-text reports, and documented the reasons for exclusion. Disagreements were resolved through discussion and consensus.

Data from the included studies were independently extracted using a standardised form. Extracted information included study objective and design, participant characteristics and sample size, intervention and comparator protocols, treatment frequency and duration, methods used to assess lymphedema, baseline and post-intervention results, follow-up periods, and authors' conclusions. The completed extraction forms were cross-checked to identify and resolve discrepancies. Extracted outcome and risk-of-bias information was managed using Microsoft Excel and Review Manager (RevMan) 5.4.1.

Quality assessment / Risk of bias analysis Risk of bias in the included randomized trials was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Because RoB 2 is result-specific, the assessment focused on the effect of assignment to intervention for the

outcome of change in upper-extremity lymphedema volume or excess arm volume at the primary post-intervention time point reported by each trial.

Two reviewers independently answered the signalling questions and assessed five domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Domain-level and overall judgements were classified as low risk of bias, some concerns, or high risk of bias according to the RoB 2 algorithms. Disagreements were resolved through discussion and consensus. Study reports, trial registry records, and published protocols were consulted when available. Traffic-light and summary plots were generated using the robvis application.

Strategy of data synthesis A meta-analysis was not performed because the included trials were not sufficiently comparable to produce a clinically meaningful pooled effect estimate. The studies evaluated different intervention contrasts, including MLD added to complete decongestive therapy versus the same treatment without MLD, decongestive lymphatic therapy containing MLD versus compression garments, and IPC added to MLD or complete decongestive therapy versus the same background treatment without IPC.

The trials also differed in intervention components and dosage, outcome definitions, measurement methods, and assessment time points. Outcomes included absolute limb volume, excess limb volume, percentage volume reduction, and circumference measured at different anatomical locations. Pooling these clinically and methodologically heterogeneous results could therefore have produced an estimate without a clear clinical interpretation.

Findings were synthesised narratively following the principles of the Synthesis Without Meta-analysis (SWiM) reporting guideline. Studies were grouped according to the intervention and comparator. For each trial, the participant characteristics, intervention protocol, comparator, treatment duration, outcome measurement, follow-up, within-group changes, and between-group findings were summarised in structured tables and accompanying text. Interpretation considered the direction and magnitude of effects, statistical estimates when reported, clinical heterogeneity, and risk-of-bias judgements, with priority given to between-group comparisons.

Subgroup analysis No formal statistical subgroup analyses were performed because only five trials were included and the studies were clinically and methodologically heterogeneous. The available evidence was insufficient to conduct reliable subgroup analyses according to participant age, lymphedema severity or duration, intervention dosage, treatment technique, or follow-up period.

Instead, studies were grouped descriptively according to their intervention contrast: MLD-containing treatment versus the same or another conservative treatment without MLD, and IPC added to MLD or complete decongestive therapy versus the same background treatment without IPC. These categories were used to structure the narrative synthesis and were not treated as statistical subgroup analyses.

Sensitivity analysis No formal sensitivity analysis was performed because the studies were not combined in a meta-analysis. Leave-one-out analyses and recalculation after excluding individual studies were therefore not applicable. A sensitivity analysis restricted to trials at low overall risk of bias was also not possible because none of the included trial results was judged to be at low risk of bias overall.

The robustness of the findings was instead considered narratively by examining whether conclusions remained consistent when interpreted in relation to study sample size, intervention and outcome heterogeneity, attrition, selective reporting, and RoB 2 judgements. All studies meeting the eligibility criteria were retained in the synthesis, while greater interpretive weight was given to studies with fewer methodological concerns.

Language restriction Studies published in English, Spanish, or Portuguese were eligible.

Country(ies) involved Chile.

Other relevant information This registration was submitted retrospectively. At the time of registration, the database searches, study selection, data extraction, risk-of-bias assessment, and narrative synthesis had been completed. The systematic review was reported according to the PRISMA 2020 statement, and the narrative synthesis was informed by the Synthesis Without Meta-analysis (SWiM) reporting guideline.

Keywords Breast cancer-related lymphedema; Upper-extremity lymphedema; Manual lymphatic drainage; Intermittent pneumatic compression;

Complex decongestive therapy; Randomized controlled trials.

Dissemination plans The primary dissemination strategy will be the presentation of the review findings at a scientific congress. The results will also be incorporated into postgraduate teaching activities and shared with students and healthcare professionals in relevant postgraduate courses. In addition, the completed manuscript will be submitted for publication to the Journal of Bodywork and Movement Therapies. The INPLASY registration number and DOI will be reported in the manuscript.

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