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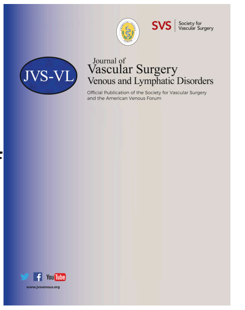

A Systematic Review of Contemporary Randomized Controlled Trials for Treatment of Lower Extremity Lymphedema by Intermittent Pneumatic Compression Devices

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A Systematic Review of Contemporary Randomized Controlled Trials for Treatment of Lower Extremity Lymphedema by Intermittent Pneumatic Compression Devices

Short Title: Systematic Review of RCTs for Lymphedema Treatment using IPC Devices

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ARTICLE HIGHLIGHTS________________

Type of Research: Systematic Review of Randomized Clinical Trials

Key Findings: This systematic review of 7 randomized controlled trials treating lymphedema of the lower extremity with IPC showed limb volume reduction in all 7 by comparison of pre versus post treatment measurements. 5/7 studies demonstrated volume reduction in the experimental arm over the control.

Take Home Message: IPC treatment reduced edema volume of the lower extremity in 177 patients in the intervention groups and 139 in the control over 7 RCTs. RCT methodological quality by risk of bias and GRADE was assessed as moderate certainty for effect.

TABLE OF CONTENTS SUMMARY____________

Seven RCTs showed that IPC treatment significantly reduced limb volume in lymphedema patients. GRADE analysis for certainty (quality of evidence) rated this has B moderate.

Abstract

Objective: Observational trials have suggested that Intermittent Pneumatic Compression (IPC) devices reduce lymphedema (LED) volume and improve patient reported outcomes (PROS), but this type of trial is subject to bias. Systematic reviews (SRs) of randomized controlled trials (RCTs) provide the highest evidentiary strength for examining the impact of a therapeutic intervention and are important for evidence-based Clinical Practice Guidelines. Few existing SRs, however, include recent RCTs and only a smaller number address LED of the lower extremities (LELED). Therefore, we conducted a SR based on PICO questions to identify RCT's, which examine the effect of IPC on lower extremity lymphedema (LELED) for a Clinical Practice Guideline.

Methods: For this SR English language RCTs in CINAHL®, Embase®, and MEDLINE® published between January 1, 2010, to January 31, 2025, were searched and the PRISMA reporting method was employed. Both intra and inter group comparisons of the specified outcome measures were examined for statistical significance. The evidentiary quality of the RCTs and risk of bias were assessed using GRADE and the Cochrane risk of bias tool (RoB 1) respectively.

Results: In the PRISMA analysis 141 articles were identified through a search of the databases and an additional four articles were discovered through other sources for a total of 145 eligible RCTs. Twenty-one RCTs addressed upper extremity LED and seven LELED RCTs met the criteria for inclusion: adults ≥18 years with unilateral or bilateral chronic lower-extremity lymphedema and present for ≥6 months and in the maintenance phase of treatment. The patient must have an ankle brachial index (ABI) ≥0.8; no active infection or acute venous thrombosis; able to use the study device and comply with daily therapy.

The average total number of patients per RCT was 54, while the mean age was 55 years. Female gender predominated (67%). The majority of RCTs were composed of secondary LED, but three

series included a segment of primary LED. Chronic venous insufficiency was the most common etiology in the seven RCT's. Five RCTs had two arms, while two had three arms. The experimental arm employed an advanced pneumatic compression device (APCD) in five RCTs, but complex decongestive therapy (CDT) was combined in this arm with IPC in three. The control comparator arm was CDT in three, a simple IPC in one and an APCD using a different mode in another. Circumferential measurement of limb girth by tape was the most common method to determine volume changes. Five of seven RCTs used a daily treatment regimen with four employing twice daily sessions. Study length varied with four weeks in three, five weeks in one and eight months in another. An a priori power calculation was carried out in 3/7 RCTs. Reduced limb volume was the outcome measure employed in all 7 studies and all 7 showed statistically significant reductions in limb volume when comparing baseline values to end of treatment values. Five RCTs also demonstrated differences in their intergroup comparisons of edema reduction. Patient reported outcomes in 5 RCTs with three generic QoL (SF-36, VAS, EQ5D3L) and two disease-specific (Lymph ICF-LL, LYMQOL) QoL measures demonstrated significant improvements by intragroup comparison in three RCTs. Heterogeneity and the composition of the experimental and control groups, however, prevented meta-analysis. The methodological quality of the 7 RCTs included in this review was evaluated using the Cochrane Risk of Bias Tool (RoB 1). Overall, the included studies demonstrated moderate methodological quality. Assessment of these RCTs by GRADE showed moderate certainty that IPC reduces lower-limb edema, volume, or circumference compared with standard care or no IPC.

Conclusion: Despite combining ("bundling") additional treatment with IPC in three studies, intragroup comparison demonstrated highly significant reductions in limb volumes with IPC in all RCTs and in 5/7 RCTs by intergroup comparison. Quality indicators demonstrated a moderate risk of bias and moderate certainty.

Keywords:

Intermittent Pneumatic Compression; Lower Extremity Lymphedema; Randomized Controlled Trials; Systematic Review; Patient Reported Outcomes; Edema, Limb Volume Reduction

Conflict of Interest / Funding Disclosures:

The authors have no conflicts of interest or funding sources to disclose.

Abbreviations:

Lymphedema (LED)

Lower Extremity Lymphedema (LELED)

Chronic Venous Insufficiency (CVI)

Breast Cancer-Related Lymphedema (BCRL)

Complete Decongestive Therapy (CDT)

Manual Lymphatic Drainage (MLD)

Intermittent Pneumatic Compression (IPC)

Advanced Pneumatic Compression Device (APCD)

Simple Pneumatic Compression Device (SPCD)

Quality of Life (QoL)

Randomized Controlled Trials (RCTs)

Patient/Problem/Population, Intervention/Exposure, Comparison/Control, Outcome (PICO)

Systematic Review (SR)

Institutional Review Board (IRB)

Body Mass Index (BMI)

Risk of Bias Tool (RoB 1)

GRADE (Grades of Recommendation, Assessment, Development, and Evaluation)

Standard of care (SOC)

Venous Leg Ulcer (VLU)

Clinical Practice Guidelines (CPGs)

Introduction

El Khoury and Bush appropriately called lymphedema (LED) "The understudied vascular condition of an under-represented population"[1] and this comment is never truer than with lower extremity lymphedema (LELED). While some epidemiologic studies suggest that chronic venous insufficiency (CVI) is the most common overall etiology of secondary lymphedema,[2] an analysis of commercial healthcare administrative claims database representing encounters with the healthcare system for diagnosis and treatment of LED show that breast cancer-related lymphedema (BCRL) [32.1%], affecting the upper extremity is twice as common as LELED (14.4%).[3] Lower extremity CVI, however, comprises the greater proportion of secondary LED (10.4%) versus cancer-related LED (4%) and is the major cause of LELED. An analysis of a similar large healthcare claims data database, IBM MarketScan, confirmed similar proportions for the etiology of secondary LED.[4]

Complete Decongestive Therapy (CDT) has been the time-honored primary treatment for LED in the initial phase.[5] This multimodal approach includes manual lymphatic drainage (MLD), compression therapy, exercise, and skin care. MLD, a specialized massage technique that helps to redirect fluid towards healthy lymphatic vessels, is characterized by slow, rhythmic, and gentle pressure applied to the skin. The goal of therapy is to reduce interstitial fluid accumulation by promoting improved drainage through the lymphatic system. Reduction of edema is associated with improvement in clinical symptoms. A systematic review of studies on MLD show mixed results.[6] LED treatment with MLD in the maintenance phase can be restricted to limited sessions by insurance coverage[7] and access to a lymphedema specialist in some areas may also be limited.[8]

Following MLD by a therapist, the patient is encouraged to perform self MLD. Patients may find it difficult to perform self MLD on a routine basis, especially the elderly who are limited in their ability to reach their lower extremities below the knee.[9] Intermittent pneumatic compression (IPC) provides a mechanical method to reduce interstitial fluid volume and can be carried out at home. Initially, simple one or two chamber IPC devices that had been used to prevent deep venous thrombosis were adapted to reduce lymphedema.[10] There are two types of *pneumatic* devices: 1) an advanced pneumatic compression device (APCD) employs an air pump to inflate and deflate multi-chambered garments, that creates sequential, gradient pressure. This device has programmable pressure levels, inflation/deflation cycles, and treatment durations; 2) a simple pneumatic compression device (SPCD), which is a similarly multi-chambered segmented device without manual control of the pressure in each chamber. A controlled prospective acute trial 40 years ago conducted in a clinical study unit with an APCD demonstrated that lower extremity volume could be reduced by 45% over initial volume measurements.[11] A long-term trial (mean 25 months) of treatment of LED with an APCD and compression stockings was associated with long-term maintenance of reduced limb girth in 90% of patients.[12]

A more recent single-arm prospective study of LELED, which used an APCD, was carried out in a veterans' population with at home treatment.[13] This study demonstrated improvement in both generic quality of life (QoL) measures and patient-reported disease specific QoL measures, while limb circumference was also reduced. Despite the findings of many studies, there are questions about efficacy that only can be validated by prospective randomized controlled trials (RCTs). It is the purpose of this study to present the results of a systematic review of IPC treatment in RCTs for LELED and an analysis of their methodological quality. This systematic review is in response to a P (Patient/Problem/Population)**,** I (Intervention/Exposure), C (Comparison/Control), O (Outcome) [PICO] question- "After initial CDT, does the addition of routine, regular IPC therapy improve outcomes in maintenance of LELED over standard of care compression therapy alone?" as part of the development of a clinical practice guideline on lower extremity lymphedema.

Methods

Selection*:* For this Systematic Review (SR) English Language RCTs in CINAHL®, Embase®, PubMed and MEDLINE® published between January 1, 2010, to January 31, 2025, were searched. Since a systematic review of existing published literature (articles) does not require Institutional Review Board (IRB) approval because it does not involve direct interaction or intervention with living human subjects or collection of new private, identifiable data, IRB approval was not obtained. Search terms and criteria for inclusion are displayed in the Appendix.

Non-randomized comparative studies and cohort studies as well as RCTs that failed to clearly define a control or experimental group were excluded. Identified RCTs were reviewed independently by two physicians (TFOD, AT). Extracted Data were recorded in a standardized Microsoft Excel spreadsheet. Data elements collected were: (1) *Patient characteristics*: Study population size, age, Gender, primary/secondary lymphedema, causes of secondary lymphedema, edema stage, and body mass index (BMI); (2) *Design characteristics*: study design, experimental group, control group, peak IPC pressure, session length, frequency and site of treatment; (3) *Outcome measures:* volume measurement method, QoL method, other outcome measure (s), and study length; (4) *Outcome results*: intragroup differences and intergroup differences in volume and quality of life. The PRISMA reporting guideline (Figure 1) was employed which provides guidance for the reporting of systematic reviews.

Assessment of the Methodologic Quality of the RCT*:* The methodological quality of the seven selected RCTs was assessed by the Cochrane Risk of Bias Tool (RoB 1), which evaluates seven standard domains: (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) completeness of outcome data, (6) selective reporting, and (7) other potential sources of bias.[14] Each domain was rated as low, unclear, or high risk of bias in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. The choice of the RoB 1 tool was dictated by the web-based platform, Covidence, that helps researchers streamline systematic reviews. This tool was employed by several of the sections performing systematic reviews in the lymphedema guideline. Covidence, however, was not employed in our systematic review.

Evidence Quality: In concert with other guidelines produced by the Society for Vascular Surgery, American Venous Forum and the American Venous and Lymphatic Society, we employed the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) framework to evaluate the quality of evidence. We used the GRADE framework to assess the Certainty of Evidence. Structured Excel tables following Cochrane Handbook guidance provided outcome-level judgements, including explicit downgrading for risk of bias, inconsistency, indirectness, imprecision, and publication bias.[15]

Results

Study Population (Figure 1): In the PRISMA analysis 141 articles were identified through a search of the databases and an additional four articles were discovered through other sources for a total of 145 eligible RCTs. Since 113 articles were not RCTs, they were excluded. Twenty-one RCTs addressed upper extremity LED treated by IPC and were excluded, while seven LELED RCTs met the criteria for inclusion in the current report.

Patient Characteristics (Table I): The overall study number of patients varied from 21 to 81 with a mean of 54 patients per study.[16 – 23] Age averaged 55 years with a range of 47 to 61 years. Female gender predominated (66.8%, 37% – 86%). The majority of the RCTs addressed secondary LED; four entirely, with three series including a portion of primary LED patients (Dunn 3%; Keeley 81%; Campisi 26%). The etiology of secondary LED was CVI in three RCTs, but importantly the cause of the secondary LED was not reported in four studies. Mean BMI in two of the studies exceeded 30 kg/m^2. Only three studies described the degree of edema by standard classification systems. All patients were in the maintenance phase of lymphedema.

Study Design Characteristics (Table II): A parallel RCT study design was used in all seven trials. Five of the seven RCTs had two arms, while two had three arms. In the experimental arm, five of the RCTs employed an APCD, while two used a SPCD- a segmented device without manual control of the pressure in each chamber. Importantly, CDT with MLD was used in addition to APCD in the experimental arm of three RCTs. In the Control arms, standard of care (SOC) was defined as CDT (with MLD) in 3 RCTs. Four RCTs each had different control groups: APCD in the sequential mode, an alternative dosing of APCD by length and frequency of treatment, no specific intervention, and a four-layer compression bandage. One study compared high pressure (120 mmHg) versus low pressure (60 mmHg) peak pressure treatment. In the remainder of the RCTs three studies used a peak pressure of approximately 40 to 50 mmHg: two 40 mmHg and one 50mmHg. Twice daily sessions were described in four RCTs. Three studies employed a session length of 60 minutes and in two sessions measured 45 to 50 minutes. Five of the seven studies prescribed daily treatment, while two applied IPC three times weekly. The length of the studies consisted of four weeks of treatment in three studies, 5 weeks in one study, 8 months in a venous leg ulcer (VLU) healing study and 1-2 weeks in two short term studies. Finally, only two of the seven carried out IPC treatment at home.

Outcomes Measure Types (Table III): Reduction in lower extremity edema was the predominant outcome measure selected in these trials and was determined by perometry in three of the RCTs and circumferential tape measurements in four. In addition, duplex ultrasound assessment of tissue thickness was employed as a concomitant measure of edema reduction in two studies. Patient reported outcome measures were carried out in 5 studies with three generic QoL and two disease-specific QoL measures. Other outcome measures employed were range of motion in two and tissue tone in one. The one study dealing with venous leg ulcers employed time to ulcer closure and healing rate to assess treatment effect.[21] Three of seven studies designated volume as a primary outcome measure.

Outcome Measures Results (Table IV): Both intra group and inter group changes in volume were carried out in the seven studies. <u>All seven studies showed a statistically significant decrease in the various objective measures of edema reduction</u> in the experimental arm when comparing pre to post final treatment measurements. No significant difference between the experimental and control arm in volume reduction (intergroup difference) was observed in the trial conducted by Alvarez[21] and Keeley (not powered to detect intergroup differences).[18] Intergroup differences were limited to the ankle and knee circumferences in deSire's study (Table IV). Taradj and colleagues' trial demonstrated that high compression pressure (120 mmHg) was superior to lower pressure (60 mmHg).[16] Dunn and colleagues employed an IPC device which simulated MLD and compared this regimen to a sequential IPC mode.[17] They observed a significant decrease in intergroup volume limited to the distal portion of the limb.[18] Finally, Campisi and associates linked significant volume reduction between the two groups ($p < 0.001$) to the number of treatment days.[19] Addressing QoL measures, including VAS, four trials (Table IV) showed a significant intra group difference comparing pre to post compression values, while two groups showed significant intergroup differences between the experimental and control groups.

Assessment of the Methodologic Quality of the RCT

Risk of Bias Assessment (Table V): The seven RCTs demonstrated moderate methodological quality. Adequate random sequence generation was reported in four of the seven trials (Tessari 2018; Alvarez 2020; de Sire 2021; Dunn 2022), while Taradaj (2015) and Campisi (2023) provided insufficient information (Table V). Moreover, Campisi (2023) used "sequential assignment" that can result in a high risk of selection bias. Allocation concealment, to prevent bias by keeping the treatment allocation hidden from researchers and participants, was generally described poorly, resulting in several unclear judgments. Performance bias was the most frequent limitation across studies, as blinding of participants and personnel was often not possible due to the recognizable features of the IPC device. Only one study (de Sire 2021) incorporated a sham IPC intervention to mitigate this bias. Similarly, blinding of outcome assessors was reported rarely. In contrast, attrition bias (Incomplete Outcome Data) and reporting bias were consistently rated as low across all studies. The use of objective outcome measures, such as limb volume, circumference, bioimpedance, however, reduced the risk of detection bias. In a summary analysis of all six domains, the majority of domains (34/42, 81%) were assessed as either low (22/42. 52%) or unclear (12/42, 29%) risk, with only a minority (8/42, 19%) high risk. The predominance of objective outcome measures and consistent reporting of complete datasets, however, enhanced the internal validity of the findings, which supported IPC as an effective intervention for reducing lower-limb edema.

GRADE: The starting level was high for these RCTs due to that trial design, and the following downgrades were applied.[15] Risk of bias was downgraded by 1 related to several factors: a few RCTs that were smaller pilot studies; most of the RCTs were not blinded, but this is not usually feasible in an intervention trial; and finally, allocation concealment was not always clearly described. There was no downgrade for inconsistency because the direction consistently favored IPC when an adequate regimen was used. Although there was heterogeneity in the population and measurement methods, it was not in the direction of the effect. Indirectness was downgraded from 0 to 0.5 related to two trials that had an active control IPC versus IPC, but the four IPC versus no IPC trials directly addressed the question. Imprecision led to a downgrade of 1 related to small sample size and limited citing of confidence intervals that reported for edema outcomes in some of the RCTs. These findings led to the conclusion by GRADE of **moderate certainty** that IPC reduces lower limb edema volume/circumference when compared with no IPC or standard care alone. This benefit, however, appears regimen dependent, while daily home use appears effective. Finally, as shown in Dunn's study[17], edema reduction diminishes and original volume reaccumulates when IPC therapy stops, implying maintenance by IPC is essential.

Discussion

This systematic review of seven RCTs in patients with predominantly secondary LED showed that IPC treatment of LELED in the experimental arm reduced limb volume in all seven trials, when baseline values were compared to end of treatment values (intragroup comparison). Statistically significant differences in reduction of edema between the experimental arm and the control group were observed in five of the seven RCTs. The predominance of objective outcome measures and consistent reporting of complete datasets as assessed by risk of bias methods enhanced the internal validity of the findings, while GRADE indicates an overall certainty of the evidence as **moderate.** These two quality measures support IPC as an effective intervention for reducing lower-limb edema. Reduction of limb volume with LELED due to excess fluid through a common protocol addresses the physical symptoms and can indirectly improve quality of life.[13, 23, 24]

This systematic review on IPC therapy was initiated as a response to a PICO question addressing IPC for developing a Clinical Practice Guideline (CPG) on LELED. CPGs define the optimal contemporary treatment of a condition based on existing evidence and as a result are a source for defining the *standard of care* for a medical condition.[25] A recent systematic review of CPGs for LED identified four CPGs, but only one CPG was published within a decade of the current analysis, indicative of a noticeable gap in contemporary LED guidelines.[26] Three of the four CPGs recommended CDT, which combines MLD, multilayer bandaging, skin care, and exercise.. In the initial (intensive) phase of therapy for lymphedema, CDT was recommended by three of the four CPGs in this systematic review. The second treatment phase of this lifelong disease, the maintenance phase, relies on the patient to carry out at-home self -management consisting of skin care, self-MLD and compression bandaging to maintain reduced limb volume and to prevent cellulitis. During the maintenance phase formal treatment with MLD by a lymphedema therapist is dependent in the United States on insurance coverage as well as the availability of therapists.[27] As a result, formal MLD may be employed less frequently in this latter phase. IPC has gained traction as a supportive tool for reduction of edema not only in the at-home maintenance phase but also when access to a lymphedema therapist is limited.

IPC devices for treatment of LED have evolved significantly over the last 75 years since the first single chamber device was introduced by Brush.[10] The subsequent development of a multi chamber sequential device[28, 29] promoted the milking of the lymph fluid from the distal portion of the limb to proximal limb segments not by venular reabsorption[30] but through existing lymphatics,[31] but peak compression pressures were still maintained at a higher range.

Currently there are two major types of IPC for treatment of lymphedema. APCDs can be programmed for different pressure levels, inflation/deflation cycles, and sequence of inflation in multiple compartments, which allows for targeted compression in specific areas. The second type, SPCD, has pre-set compression levels and cycles, with limited user control, which may not offer the ability to program or adjust settings. As a result, SPCD provides a fixed treatment protocol. Fife and colleagues' RCT compared limb volume changes by an APCD versus a SCPD in upper extremity LED over a 3-month period.[32] The APCD group showed statistically superior results in volume reduction over the SCPD group.

LED can be more difficult to treat in the legs than in the arms, because gravity plays a major role both by enhancing edema formation with increasing capillary filtration pressure and the burden of pumping lymph fluid proximally "uphill". Moreover, CVI, the commonest cause of LED in the lower extremities, affects two vascular systems. Despite correction of the venous hypertension by ablation or stenting procedures, LED persists in approximately 40% of these treated patients with phlebolymphedema.[33]

LELED is studied less. A recent systematic review documented fewer randomized controlled trials of either IPC (4/15, 27%) or MLD (4/20, 20%) therapy for the lower extremities than for the upper extremities.[34] In addition, the cause of the secondary upper extremity LED is more singular due to BCRL than that of lower extremity LED, where CVI, morbid obesity and cancer are causes in varying proportions.

Upper extremity lymphedema is treated differently than lower extremity lymphedema in both the utilization of conservative therapy and the specific type of conservative therapy (CDT or IPC).[3] While upper extremity BCRL patients receive some form of conservative therapy 94% of the time, a lesser proportion of the CVI patients (82%) underwent treatment resulting in a “treatment gap” of 12% for the latter group. The difference between treatment of upper and lower extremity LED is further magnified by use of the individual components of conservative therapy.

Of BCRL patients 72% received MLD, but a lower 12.5% underwent IPC therapy.[35] By contrast, treatment of advanced CVI patients (9.6% of study patients) by MLD was nearly one half (34%) that of the BCRL group, but IPC therapy was nearly threefold higher in the advanced CVI group (36%) than in BCRL. Noticeably, in the four reviewed CPG's reviewed IPC treatment was not mentioned in one and recommendations for this treatment were based on older studies.[26]

Numerous retrospective studies of varying evidentiary quality explored the benefits of IPC in treating patients with lower extremity lymphedema and have shown promising results.[36-38] A large recent prospective longitudinal study of 180 veterans with LELED, who were followed for a year undergoing at home APCD treatment, showed an improvement in both generic and disease specific QoL as well as reduction in calf circumference.[13] There was no comparator group in this study. As a result, in the evidence hierarchy this study would be judged to be less impactful than a RCT despite the large patient population, prospective design and the 12-month study length.

Systematic reviews of randomized controlled trials provide the highest quality of evidence and as such they are the cornerstone of clinical practice guidelines. Our systematic review of seven RCTs treating lymphedema in the lower extremity with IPC showed some clinically relevant findings. RCTs prospectively assess the effectiveness of a new intervention versus a control group, which most frequently is the current standard of care. This study design has important characteristics: reduces potential bias, rigorously examines the relationship between a new intervention and a specified outcome is critical for evaluating the evidentiary strength of these trials. For applicability, RCTs should simulate current clinical treatment protocols, so that that the selection of an appropriate control group is critical. Usually the control group is the "best contemporary" treatment and is frequently derived from existing CPGs. CDT, as SOC, was employed in three studies in this systematic review for the control group, while four-layer bandages were appropriately SOC in a VLU population.

All seven RCTs showed a statistically significant improvement in post-treatment volume reduction for the experimental arm over baseline (*intragroup* comparison), while five of the seven studies, exhibited significant reduction in edema by an *intergroup* comparison of the experimental arm to the control [Table IV]. Three studies addressed how IPC should be delivered for superior edema reduction. Keeley's unique comparison of "dosing frequency" for APCD treatment showed that a regimen of one hour per day was superior to two hours a day for edema reduction.[18] Taradj's trial suggested that higher pressure for compression was better than lower pressure.[15] Finally, an IPC device which simulated MLD was shown to be superior to treatment by standard graduated sequential IPC.[16] Three RCTs [Table II] employed "bundling" in the experimental arm where two interventions were combined in the experimental arm, such as IPC with MLD or with CDT.[19, 22] However, this approach "*makes it difficult to determine the contribution of each individual component of treatment to the outcomes achieved*".[39] This factor contributes to heterogeneity in the experimental arm which prevented a meta-analysis along with other sources of heterogeneity such as differences in the frequency of treatment and its duration, length of the compression cycle, peak pressure, and site of treatment.

Assessing both risk of bias and GRADE provides a critical analysis of these RCTs to confirm their methodologic rigor and transparency. Most importantly, these methodological flaws may promote an overestimation or underestimation of treatment effects. These flaws can lead to incorrect clinical conclusions which are extremely important especially if the systematic review is the basis for clinical practice guidelines. In a summary analysis of all six domains by the RoB 1 tool the majority of domains (34/42, 81%) were assessed as either low (22/42. 52%) or unclear (12/42, 29%) risk, with only a minority (8/42, 19%) high risk. Moreover, the predominance of objective outcome measures and consistent reporting of complete datasets enhanced the internal validity of the findings, which supporting IPC as an effective intervention for reducing lower-limb edema.

The other tool evaluating methodologic quality, GRADE, provides a rating of the certainty of evidence for each outcome. For the IPCs in this systematic review the outcome was reduction of limb volume/edema with treatment. GRADE assesses the confidence that a reviewer can place that the observed treatment effect reflects the **true** effect. This is accomplished by assessing factors within the respective RCTs, such as risk of bias, inconsistency in precision and publication bias. The result is a reliable recommendation on the quality of evidence in a guideline. Our analysis by GRADE showed **moderate certainty** that IPC reduces LELED when compared to no IPC or standard care alone.

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Table I. Patient Characteristics

STUDY (n=7)	NUMBER	AGE (YRS)	GENDER (%F)	PRIMARY/ SECONDARY	CAUSE	EDEMA STAGE	BMI
TARADJ 2015	81	51.5	58.6	SECONDARY	100% - CVI	80% II, III BRUNNER	ALL <28
TESSARI* 2018	50	58	72	SECONDARY	68% - LED 32% - CVI	NR	42% >30
ALVAREZ 2020	52	NR	NR	SECONDARY	VLU	NR	NR
deSIRE 2021	30	54	37	SECONDARY	NR	II-IV ISL	27
DUNN 2022	40	61	75	PRIMARY 2.5% SECONDARY	NR	80% - II ISL	36
KEELEY 2023	21	58	86	PRIMARY 81%	PRIMARY	NR	29
CAMPISI 2023	50	47	72	SECONDARY 74%	PRIMARY 26% NR 2*	NR	NR

NR, not reported; CVI, chronic venous insufficiency; VLU, venous leg ulcer; ISL, International Society for Lymphology; YRS, years; %F, percentage female; LED, Lymphedema

Table II. Study Design Characteristics

STUDY (n=7)	DESIGN	EXPERIM	CONTROL	PRESSURE	SESSION LENGTH	FREQU	SITE
TARADJ 2015	P 3 ARMS	APCD HI/LO +MLD	CDT NO IPC	120 TORR 60 TORR	45 MIN	3/WEEK X 4WKS	OPD
TESSARI 2018	P 2 ARMS	SPCD	NO INTV'N	50 TORR	50 MIN BID	DAILY 4 WKS	OPD
ALVAREZ 2020	P 2 ARMS	SPCD	4 LB	40-50 TORR	60 MIN BID	8 MOS	HOME
deSIRE 2021	P 2 ARMS	APCD/MLD BILAT	SAME MLD SHAM IPC	60-80 TORR	30 MLD 60 IPC	3/WEEK 4 WKS	OPD
DUNN 2022	P 2 ARMS	APCD	SEQUENT'L	40 TORR	BID NO TIME	DAILY 5 WKS	HOME
KEELEY 2023	P 3 ARMS	APCD 1 HR/DAY 2 60 MIN/DAY	2X 2 HR/DAY	30-40 TORR	VARIED 60 OR BID	12 DAYS A 5 DAYS B.C	OPD
CAMPISI 2023	P 2 ARMS	APCD/CDT	CDT	45-50 TORR	60 MIN BID	DAILY 11 DAYS + 20 DAYS	OPD

ACPD, Advanced Pneumatic Compression Device; SPCD, Simple Pneumatic Compression Device; MLD, manual lymphatic drainage; BILAT, bilateral application; HR, Hour; MIN, minutes; CDT, Complex Decongestive Therapy; BID, twice daily; OPD, outpatient site; HI, high pressure; LO, low pressure; EXPERIM, experiment; INTV'N, intervention; SEQUENT'L, sequential; FREQU, frequency; P, Parallel

Table III. Outcome Measure Types

STUDY (n=7)	VOLUME	GIRTH DUS THICKNESS	QoL	OTHER	EXPRESSED	PRIMARY	EVAL'N
TARADJ 2015	PEROM		NO	NONE	ABS VOL ↓ % REDUX'N	NO	1 MONTH
TESSARI 2018	H_2O	CIRC DUS	SF-36	ROM	ABS VOL ↓ CIRC SubQ THICKNESS	NO	1 MONTH
ALVAREZ 2020		ANKLE/CALF CIRC ONLY	VAS	TIME TO HEAL'N, RATE	ABS VOL REDUX'N % REDUX'N	NO	8 MONTHS
deSIRE 2021		CIRC ONLY 5 SITES	EQ5D3L EQ-VAS	ROM	CIRC SITE → ABS CIRC REDUX'N	YES	1 MONTH
DUNN 2022		CIRC → VOL CALC'N	LYMPH-ICF-LL	NONE	CIRC CALC'N ABS VOL ↓ TOTAL, DIST, PROX	YES VOL	5 WEEKS
KEELEY 2023	PEROM	DUS BIS/TDC	LYMQoL	TISSUE TONE	ABS VOL REDX'N	NO	5 DAYS A 7 DAYS
CAMPISI 2023	PEROM		NO	NONE	% CHANGE LIMB VOL	YES VOL	11 DAYS + 20 DAYS

PEROM, Perometry; DUS, duplex ultrasound of tissue thickness; CIRC, circumferential measurements; H_2O, water displacement; TDC, tissue dielectric constant; VAS, visual analog scale; ROM, range of motion; HEAL'N, healing; ABS, absolute change; VOL, volume; REDUX'N. reduction; CALC'N, calculation; PROX, proximal; DIST, distal; EVAL'N, evaluation; SubQ, Subcutaneous; BIS, Bioimpedance Spectroscopy

Table IV. Outcomes of randomized controlled trials evaluating intermittent pneumatic compression for lymphedema: intra-group change from baseline and inter-group differences between experimental and control groups

Study	Analysis	Volume	Girth	Thickness (DUS)	Pain	Quality of life
Taradaj 2015	Intra-group	Abs: A −5668, B −2051, C −1722 all*** (% decrease A38.5, B13.1, C11.9)**	NR	NR	NR	NR
	Inter-group	% decrease A > B and C****; B = C (NS)	NR	NR	NR	NR
Tessari 2018	Intra-group	Abs E −181, **** C +117	E decreased at all 6 sites***	E decreased at all 8 sites	NR	Generic QoL improved 4/8*
	Inter-group	E vs C (NS)	E > C at 4/6 sites***	E > C at all 6 sites*,**	NR	NS
Alvarez 2020	Intra-group	NP	E, Ankle −19.1%, calf −18.7%*	NR	VAS improvement*	NR
	Inter-group	NP	NS	NR	VAS E > C*	NR
de Sire 2021	Intra-group	NP	E, Abs decrease at all 6 sites****	NR	NR	Generic QoL improved**
	Inter-group	NP	E > C at 3/5 sites****	NR	NR	E > C***

Dunn 2022	Intra-group	E & C Abs Distal & proximal, total −***	Calculated limb volume	NR	NR	Disease-specific QoL improved***
	Inter-group	E, Abs Distal reduction only**	NR	NR	NR	NS
Keeley 2023	Intra-group	E, 1Hr/day Abs −87** (1.24%)	NR	NR	NR	Disease-specific QoL NS
	Inter-group	NS	NR	NR	NR	NS
Campisi 2023	Intra-group	Abs: E −1035.7, C −474.9**** (% reduction 11.7 vs 6) C Stat NR	NR	NR	NR	NR
	Inter-group	% reduction E > C****	NR	NR	NR	NR

Taradj: Group A, 120 Torr: Group B, 60 Torr; DUS, duplex ultrasound; E, experimental group; C, control group; Abs, Absolute reduction; -, decrease; +, increase; VAS, visual analog scale; QoL, quality of life; NP, not performed; NR, not reported; NS, not significant. Significance levels: *P < .05; **P < .01; ***P < .001; ****P < .0001.

Table V. Risk of Bias Assessment (RoB 1)

STUDY (n=7)	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS & PERSONNEL	BLINDING OF OUTCOME ASSESSORS	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING
TARADJ 2015	UNCLEAR RISK	UNCLEAR RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK

TESSARI 2018	LOW RISK	LOW RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK
ALVAREZ 2020	LOW RISK	LOW RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK
deSIRE 2021	LOW RISK	UNCLEAR RISK	LOW RISK	UNCLEAR RISK	LOW RISK	LOW RISK
DUNN 2022	LOW RISK	UNCLEAR RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK
KEELEY 2023	LOW RISK	UNCLEAR RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK
CAMPISI 2023	HIGH RISK	HIGH RISK	HIGH RISK	UNCLEAR RISK	LOW RISK	LOW RISK

IPC RCTs

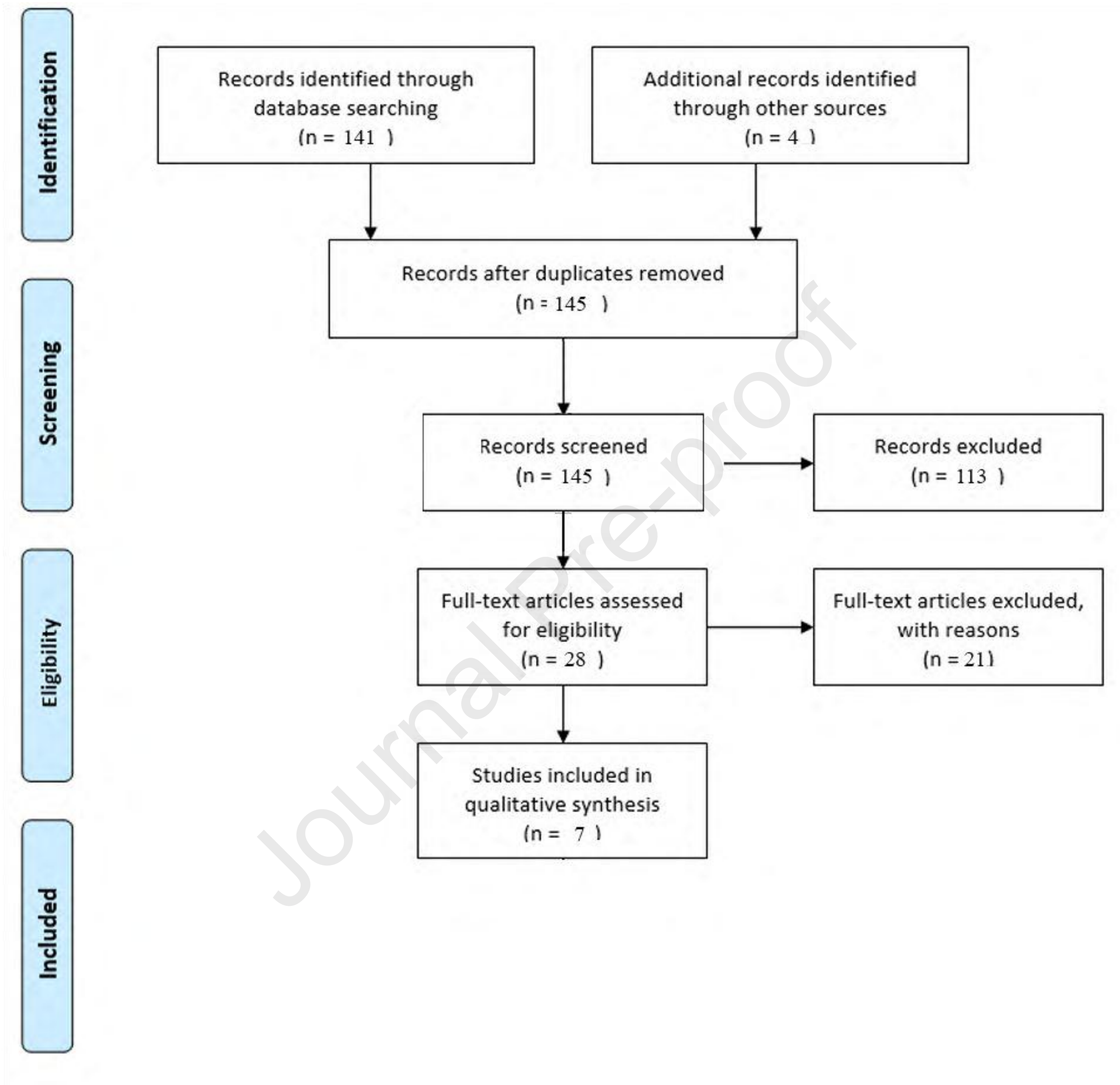
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 141)
Additional records identified through other sources (n = 4)
Records after duplicates removed (n = 145)
Records screened (n = 145)
Records excluded (n = 113)
Full-text articles assessed for eligibility (n = 28)
Full-text articles excluded, with reasons (n = 21)
Studies included in qualitative synthesis (n = 7)

Figure & Table Legend

Figure 1: PRISMA flow diagram summarizing the flow of the screening process.

Table I. Patient Characteristics

NR, not reported; CVI, chronic venous insufficiency; VLU, venous leg ulcer; ISL, International Society for Lymphology; YRS, years; %F, percentage female; LED, Lymphedema

Table II. Study Design Characteristics

ACPD, Advanced Pneumatic Compression Device; SPCD, Simple Pneumatic Compression Device; MLD, manual lymphatic drainage; BILAT, bilateral application; HR, Hour; MIN, minutes; CDT, Complex Decongestive Therapy; BID, twice daily; OPD, outpatient site; HI, high pressure; LO, low pressure; EXPERIM, experiment; INTV'N, intervention; SEQUENT'L, sequential; FREQU, frequency; P, Parallel

Table III. Outcome Measure Types

PEROM, Perometry; DUS, duplex ultrasound of tissue thickness; CIRC, circumferential measurements; H2O, water displacement; TDC, tissue dielectric constant; VAS, visual analog scale; ROM, range of motion; HEAL'N, healing; ABS, absolute change; VOL, volume; REDUX'N. reduction; CALC'N, calculation; PROX, proximal; DIST, distal; EVAL'N, evaluation; SubQ, Subcutaneous; BIS, Bioimpedance Spectroscopy

Table IV. Outcome Measures Results

COMP, Comparison; INTRA, baseline vs final; INTER, experimental vs control; PROX, proximal; DIST, distal; ABS, absolute change; %, percent; DEC, decrease; INC, increase; DUS, duplex ultrasound; VAS, visual analog scale; CALC'N, calculation; VOL, volume; QoL, quality of life; Gen, generic; DS, disease-specific; NP, not performed; NR, not reported; NS, not significant. Significance: *P<.05; **P<.01; ***P<.001; ****P<.0001.

Table V. Risk of Bias Assessment (RoB 1)