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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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ABSTRACT

Objective: Observational trials have suggested that intermittent pneumatic compression (IPC) devices reduce lymphedema (LED) volume and improve patient-reported outcomes, 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 RCTs that examined the effect of IPC on LELED for a clinical practice guideline.

Methods: For this SR, English-language RCTs in CINAHL, Embase, and MEDLINE published between January 1, 2010, and January 31, 2025, were searched and the PRISMA reporting method was used. Both intragroup and intergroup 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, respectively.

Results: In the PRISMA analysis, 141 articles were identified through a search of the databases and an additional 4 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 LELED and present for ≥6 months and in the maintenance phase of treatment. The patient must have an ankle-brachial index of ≥0.8, have no active infection or acute venous thrombosis, and be able to use the study device and comply with daily therapy. The average total number of patients per RCT was 54, and the mean patient 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 RCTs. Five RCTs had two arms, and two had three arms. The experimental arm used an advanced pneumatic compression device in five RCTs, but complex decongestive therapy was combined in this arm with IPC in three. The control comparator arm was complex decongestive therapy in three, a simple IPC in one, and an advanced pneumatic compression device 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 using twice daily sessions. Study length varied with 4 weeks in three, 5 weeks in one, and 8 months in another. An a priori power calculation was carried out in three of the seven RCTs. Reduced limb volume was the outcome measure used in all seven studies and all seven showed statistically significant reductions in limb volume when comparing baseline values with end-of-treatment values. Five RCTs also demonstrated differences in their intergroup comparisons of edema reduction. Patient-reported outcomes in five RCTs with three generic quality-of-life (Short Form-36, visual analog scale, and EQ5D3L) and two disease-specific (Lymph ICF-LL and LYMQOL) quality-of-life 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 seven RCTs included in this review was evaluated using the Cochrane Risk of Bias Tool. 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.

Conclusions: Despite combining (bundling) additional treatment with IPC in three studies, intragroup comparisons demonstrated highly significant reductions in limb volumes with IPC in all RCTs and in five of seven RCTs by intergroup comparison. Quality indicators demonstrated a moderate risk of bias and moderate certainty. (J Vasc Surg Venous Lymphat Disord 2026;14:102500.)

Keywords: Intermittent pneumatic compression; Lower extremity lymphedema; Randomized controlled trials; Systematic review; Patient-reported outcomes; Edema; Limb volume reduction

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El Khoury and Bush[1] appropriately called lymphedema (LED) "The understudied vascular condition of an underrepresented population," and this comment is never truer than with lower extremity LED (LELED). Most epidemiological studies suggest that cancer treatment is the most common overall etiology of non filariasis related secondary LED.[2] For example an analysis of commercial health care administrative claims database representing encounters with the health care system for diagnosis and treatment of LED showed that breast cancer-related LED (BCRL) (32.1%), affecting the upper extremity, is twice as common as LELED (14.4%).[3] Lower extremity chronic venous insufficiency (CVI), however, comprises overall the greater proportion of secondary LED (10.4%) and is the major cause of LELED. An analysis of a similar large health care 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 toward 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 (SR) of studies on MLD show mixed results.[6] LED treatment with MLD in the maintenance phase can be restricted by insurance coverage[7] and access to a LED specialist in some areas may also be limited.[8]

After 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 LED.[10] There are two types of pneumatic devices: (1) an advanced pneumatic compression device (APCD) uses an air pump to inflate and deflate multichambered garments, that creates sequential, gradient pressure. This device has programmable pressure levels, inflation/deflation cycles, and treatment durations. (2) There is also a simple pneumatic compression device (SPCD), which is a similarly multichambered 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, whereas 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 SR of IPC treatment in RCTs for LELED and an analysis of their methodological quality. This SR 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 (SOC) compression therapy alone?" as part of the development of a clinical practice guideline (CPG) on LELED.

ARTICLE HIGHLIGHTS

- **Type of Research:** Systematic review of randomized clinical trials
- **Key Findings:** This systematic review of seven randomized controlled trials (RCTs) treating lymphedema of the lower extremity with intermittent pneumatic compression showed limb volume reduction in all seven by comparison of pretreatment vs post-treatment measurements. Five of the seven studies demonstrated volume reduction in the experimental arm over the control.
- **Take Home Message:** Intermittent pneumatic compression treatment reduced edema volume of the lower extremity in 177 patients in the intervention groups compared to 139 in the control over 7 RCTs. RCT methodological quality by risk of bias and GRADE was assessed as moderate certainty for effect.

METHODS

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

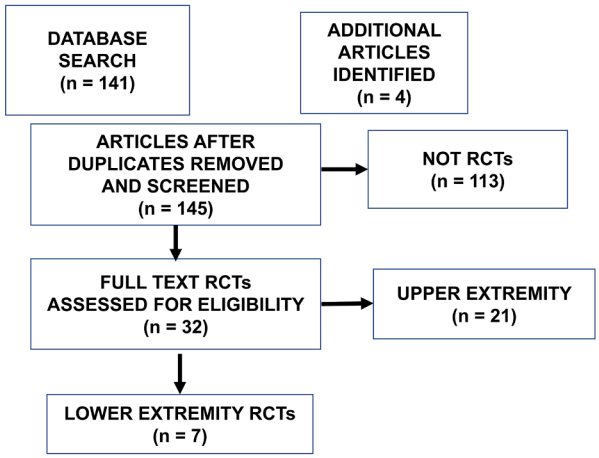


Fig. PRISMA flow diagram summarizing the flow of the screening process.

Nonrandomized 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 (T.F.O'D., A.T.). Extracted data were recorded in a standardized Microsoft Excel spreadsheet. Data elements collected were: (1) patient characteristics: study population size, age, gender, primary/secondary LED, causes of secondary LED, edema stage, and body mass index; (2) design characteristics: study design, experimental group, control group, peak IPC pressure, session length, and frequency and site of treatment; (3) outcome measures: volume measurement method, QoL method, other outcome measure (s), and study length; and (4) outcome results: intragroup differences and intergroup differences in volume and QoL. The PRISMA reporting guidelines (Fig) were used, which provide guidance for the reporting of SRs.

Assessment of the Methodological 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, which helps researchers to streamline SRs. This tool was used by several of the sections performing SRs in the LED guideline. Covidence, however, was not used in our SR.

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 used the GRADE 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 judgments, including explicit downgrading for risk of bias, inconsistency, indirectness, imprecision, and publication bias.[15]

RESULTS

Study population

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 (Figure). Because 113 articles were not RCTs, they were excluded. Twenty-one RCTs addressed upper extremity LED treated by IPC and were excluded; seven LELED RCTs met the criteria for inclusion in the current report.

Patient characteristics

The overall study number of patients varied from 21 to 81 with a mean of 54 patients per study (Table I).[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 et al,[16] 3%; Keeley et al,[17] 81%; and Campisi et al,[19] 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. The mean body mass index 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 LED.

Study design characteristics

A parallel RCT study design was used in all seven trials (Table II). Five of the seven RCTs had two arms, and two

Table I. Patient characteristics

Study (n = 7)	Number	Age, years	Female sex, %	Primary/ secondary	Cause	Edema stage	BMI
Taradaj 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
de Sire 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

BMI, Body mass index; *CVI*, chronic venous insufficiency; *ISL*, International Society for Lymphology; *NR*, not reported; *LED*, lymphedema; *VLU*, venous leg ulcer.
2*, No causes of secondary LED provided.

had three arms. In the experimental arm, five of the RCTs used an APCD, whereas two used an SPCD-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, SOC was defined as CDT (with MLD) in three 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 mm Hg) vs low-pressure (60 mm Hg) peak pressure treatment. In the remainder of the RCTs, three studies used a peak pressure of approximately 40 to 50 mm Hg: two 40 mm Hg and one 50 mm Hg. Twice daily sessions were described in four RCTs. Three studies used a session length of 60 minutes and in two sessions measured 45 to 50 minutes. Five of the seven studies prescribed daily treatment, and two applied IPC three times weekly. The length of the studies consisted of 4 weeks of treatment in three studies, 5 weeks in one study, 8 months in a venous leg ulcer healing study, and 1 to 2 weeks in two short-term studies. Finally, only two of the seven studies carried out IPC treatment at home.

Outcomes measure types

A decrease 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 (Table III). In addition, duplex ultrasound assessment of tissue thickness was used as a concomitant measure of edema reduction in two studies. Patient-reported outcome measures were carried out in five studies, with three generic QoL and two disease-specific QoL measures. Other outcome measures used were range of motion in two and tissue tone in one. The one study dealing with venous leg ulcers used time to ulcer closure and healing rate to assess treatment effect.[21] Three of the seven studies designated volume as a primary outcome measure.

Outcome measures results

Both intragroup and intergroup changes in volume were carried out in the seven studies (Table IV). All seven studies showed a statistically significant decrease in the various objective measures of edema reduction in the experimental arm when comparing pre with 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 et al[21] and Keeley et al[18] (not powered to detect intergroup differences). Intergroup differences were limited to the ankle and knee circumferences in de Sire's study (Table IV). Taradaj et al's trial[16] demonstrated that high compression pressure (120 mm Hg) was superior to lower pressure (60 mm Hg). Dunn et al[17] used an IPC device which simulated MLD and compared this regimen with a sequential IPC mode. They observed a significant decrease in intergroup volume limited to the distal portion of the limb.[18] Finally, Campisi et al[19] linked significant volume reduction between the two groups ($P < .001$) to the number of treatment days. Addressing QoL measures, including visual analog scale, four trials (Table IV) showed a significant intragroup difference comparing pre with post compression values, whereas two groups showed significant intergroup differences between the experimental and control groups.

Table II. Study design characteristics

Study (n = 7)	Design	Experiment	Control	Pressure	Session length	Frequency	Site
Taradaj 2015	P 3 arms	APCD hi/lo +MLD	CDT no IPC	120 torr 60 torr	45 minutes	3/wk × 4 wk	OPD
Tessari 2018	P 2 arms	SPCD	No intervention	50 torr	50 minutes BID	Daily × 4 wk	OPD
Alvarez 2020	P 2 arms	SPCD	4 lb	40-50 torr	60 minutes BID	8 mo	Home
de Sire 2021	P 2 arms	APCD/MLD bilateral application	Same MLD sham IPC	60-80 torr	30 MLD 60 IPC	3 × wk × 4 wk	OPD
Dunn 2022	P 2 arms	APCD	Sequential	40 torr	BID NO TIME	Daily × 5 wk	Home
Keeley 2023	P 3 arms	APCD 1 HR/DAY 2× 60 min/d	2 × 2 h/d	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 minutes BID	Daily 11 days +20 days	OPD

ACPD, Advanced pneumatic compression device; *BID*, twice daily; *CDT*, complex decongestive therapy; *hi*, high pressure; *OPD*, outpatient site; *lo*, low pressure; *MLD*, manual lymphatic drainage; *P*, parallel; *SPCD*, simple pneumatic compression device.

Table III. Outcome measure types

Study (n = 7)	Volume	Girth DUS thickness	QoL	Other	Expressed	Primary	Evaluation
Taradaj 2015	Perometry		No	None	ABS volume ↓ % reduction	NO	1 month
Tessari 2018	H_2O	Circumferential measurements DUS	SF-36	ROM	ABS volume ↓ circumferential measurements SubQ thickness	NO	1 month
Alvarez 2020		Ankle/calf circumferential measurements only	VAS	Time to healing, Rate	ABS volume reduction % reduction	NO	8 months
de Sire 2021		Circumferential measurements only 5 sites	EQ5D3L EQ-VAS	ROM	Circumferential measurements site → ABS circumferential measurements reduction	Yes	1 month
Dunn 2022		Circumferential measurements → volume CALC'N	LYMPH-ICF-LL	None	Circumferential measurements calculation ABS volume ↓ total, distal, proximal	Yes volume	5 weeks
Keeley 2023	Perometry	DUS BIS/TDC	LYMQoL	Tissue Tone	ABS volume reduction	no	5 days A 7 days
Campisi 2023	Perometry		No	None	% change LIMB volume	yes Volume	11 days +20 days

ABS, absolute change; *BIS*, bioimpedance spectroscopy; *DUS*, duplex ultrasound of tissue thickness; *H_2O*, water displacement; *ROM*, range of motion; *SubQ*, subcutaneous; *TDC*, tissue dielectric constant; *VAS*, visual analog scale.

Assessment of the methodological quality of the RCTs

Risk of bias assessment. The seven RCTs demonstrated moderate methodological quality (Table V). Adequate random sequence generation was reported in four of the seven trials (Tessari et al 2018[20]; Alvarez et al 2020[21]; de Sire et al 2021[22]; Dunn et al 2022[17]), whereas Taradaj et al[15] (2015) and Campisi et al[19] (2023) provided insufficient information (Table V). Moreover, Campisi et al[19] (2023) used sequential assignment, which 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 common limitation across studies, as blinding of participants and personnel was often not possible owing to the recognizable features of the IPC device. Only one study (de Sire et al 2021[22]) incorporated a sham IPC

Table IV. Outcomes of randomized controlled trials (RCTs) evaluating intermittent pneumatic compression (IPC) for lymphedema (LED): Intragroup change from baseline and inter-group differences between experimental and control groups

Study	Analysis	Volume	Girth	Thickness (DUS)	Pain	QoL
Taradaj 2015	Intragroup	Abs: A −5668, B −2051, C −1722 all[c] (% decrease A38.5, B13.1, C11.9)[b]	NR	NR	NR	NR
	Intergroup	% decrease A > B and C[d]; B = C (NS)	NR	NR	NR	NR
Tessari 2018	Intragroup	Abs E −181,[d] C +117	E decreased at all 6 sites[c]	E decreased at all 8 sites	NR	Generic QoL improved 4/8[a]
	Intergroup	E vs C (NS)	E > C at 4/6 sites[c]	E > C at all 6 sites[a,b]	NR	NS
Alvarez 2020	Intragroup	NP	E, ankle −19.1%, calf −18.7%[a]	NR	VAS improvement[a]	NR
	Intergroup	NP	NS	NR	VAS E > C[a]	NR
de Sire 2021	Intragroup	NP	E, Abs decrease at all 6 sites [d]	NR	NR	Generic QoL improved[b]
	Intergroup	NP	E > C at 3/5 sites [d]	NR	NR	E > C[c]
Dunn 2022	Intragroup	E and C Abs distal and proximal, total −[c]	Calculated limb volume	NR	NR	Disease-specific QoL improved[c]
	Intergroup	E, Abs distal reduction only[b]	NR	NR	NR	NS
Keeley 2023	Intragroup	E, 1 h/d Abs −87[b] (1.24%)	NR	NR	NR	Disease-specific QoL NS
	Intergroup	NS	NR	NR	NR	NS
Campisi 2023	Intragroup	Abs: E −1035.7, C −474.9 [d] (% reduction 11.7 vs 6.0) C Stat NR	NR	NR	NR	NR
	Intergroup	% reduction E > C[d]	NR	NR	NR	NR

Taradaj: group A, 120 Torr; group B, 60 Torr.
−, Decrease; +, increase; *Abs*, absolute reduction; *C*, control group; *DUS*, duplex ultrasound; *E*, experimental group; *NP*, not performed; *NR*, not reported; *NS*, not significant; *QoL*, quality of life; *VAS*, visual analog scale.
[a] $P < .05$.
[b] $P < .01$.
[c] $P < 01$.
[d] $P < .0001$.

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, decreased 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 owing 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 0.0 to 0.5 related to two trials that had an active control IPC vs IPC, but the four IPC vs no IPC trials directly addressed the question.

Table V. Risk of bias assessment (RoB 1)

Study (n = 7)	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting
Taradaj 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
de Sire 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

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 to be regimen dependent, whereas daily home use appears to be effective. Finally, as shown in Dunn et al's study,[17] edema reduction diminishes and original volume reaccumulates when IPC therapy stops, implying maintenance by IPC is essential.

DISCUSSION

This SR 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 with 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, whereas GRADE indicates an overall certainty of the evidence as moderate. These two quality measures support IPC as an effective intervention for decreasing lower limb edema. Reduction of limb volume with LELED owing to excess fluid through a common protocol addresses the physical symptoms and can indirectly improve QoL.[13,23,24]

This SR on IPC therapy was initiated as a response to a PICO question addressing IPC for developing a 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 SOC for a medical condition.[25] A recent SR 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 LED, CDT was recommended by three of the four CPGs in this SR. 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 LED therapist depends in the United States on insurance coverage as well as the availability of therapists.[27] As a result, formal MLD may be used 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 an LED therapist is limited.

IPC devices for the 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 multichamber 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]; however, peak compression pressures were still maintained at a higher range.

Currently, there are two major types of IPC for treatment of LED. 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 preset 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 et al's RCT[32] compared limb volume changes by an APCD vs a SCPD in upper extremity LED over a 3-month period. 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 less studied. A recent SR documented fewer RCTs 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 owing to BCRL than that of LELED, where CVI, morbid obesity, and cancer are causes in varying proportions.

Upper extremity LED is treated differently than LELED in both the utilization of conservative therapy and the specific type of conservative therapy (CDT or IPC).[3] Although 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 LELED is further magnified by use of the individual components of conservative therapy.

Of BCRL patients, 72% received MLD; however, 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 three-fold higher in the advanced CVI group (36%) than in the BCRL group. Noticeably, in the four reviewed CPGs, 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 have explored the benefits of IPC in treating patients with LELED and have hown promising results.[36-38] A large recent prospective longitudinal study of 180 veterans with LELED, who were followed for 1 year undergoing at-home APCD treatment, showed an improvement in both generic and disease-specific QoL, as well as a decrease 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.

SRs of RCTs provide the highest quality of evidence; as such, they are the cornerstone of CPGs. Our SR of seven RCTs treating LED in the lower extremity with IPC showed some clinically relevant findings. RCTs prospectively assess the effectiveness of a new intervention vs a control group, which most frequently is the current SOC. This study design has important characteristics: it 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 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 the SOC, was used in three studies in this SR for the control group, although four-layer bandages were appropriately used in the SOC for a venous leg ulcer population.

All seven RCTs showed a statistically significant improvement in post-treatment volume reduction for the experimental arm over baseline (intragroup comparison), and five of the seven studies exhibited a 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 et al's[18] unique comparison of dosing frequency for APCD treatment showed that a regimen of 1 hour per day was superior to 2 hours a day for edema reduction. Taradaj et al's trial[15] suggested that higher pressure for compression was better than lower pressure. Finally, an IPC device that simulated MLD was shown to be superior to treatment by standard graduated sequential IPC.[16] Three RCTs (Table II) used 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 methodological rigor and transparency. Most important, 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 SR is the basis for CPGs. 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 support IPC as an effective intervention for decreasing lower-limb edema.

The other tool evaluating methodological quality, GRADE, provides a rating of the certainty of evidence for each outcome. For the IPCs in this SR 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 decreases LELED when compared with no IPC or standard care alone.

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