Pneumatic Compression Device Treatment of Lower Extremity Lymphedema Elicits Improved Limb Volume and Patient-reported Outcomes

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WHAT THIS PAPER ADDS

Lower extremity (LE) lymphedema is common and highly morbid, but a major knowledge gap exists in the evidence defining optimal treatment strategies. Pneumatic compression devices (PCDs) represent one potentially beneficial component of an effective multimodality approach to LE lymphedema. This study represents the largest study of PCD treatment outcomes in LE patients. These data demonstrate that use of an advanced PCD (APCD) is associated with significant limb volume reduction, which was associated with improvement in quality of life and no significant adverse effects. The study provides confidence that APCD use may beneficially influence treatment outcomes for patients with LE lymphedema.

Objectives: Examine the effectiveness of an advanced pneumatic compression device (APCD) in reducing limb volume (LV), and to evaluate clinician and patient-reported outcomes.
Design: Device registry study.
Materials and methods: Data were collected prospectively for 196 lower extremity lymphedema patients prescribed an APCD. Baseline and post-treatment LVs were calculated and clinical outcomes (skin changes, pain, and function) were assessed. Patient-reported outcomes and satisfaction utilizing a pre- and post-treatment survey were also evaluated.
Results: 90% of APCD-treated patients experienced a significant reduction in LV with 35% enjoying a reduction >10%. Mean LV reduction was 1,150 mL or 8% ($p < .0001$). Greater baseline LV and BMI were strong predictors of LV reduction ($p < .0001$). Clinician assessment indicated that the majority of patients experienced improvement in skin fibrosis and function. Patient-reported outcomes showed a significant increase in ability to control lymphedema through APCD treatment, with an increase in function and a reduction in the interference of pain. 66% were "very satisfied" with the APCD treatment.
Conclusion: APCD use is associated with consistent reductions in LV, with favorable patient-reported outcomes. Results demonstrate that reduction in LV and pain, combined with functional improvement and patient satisfaction can be achieved, providing tangible benefit for lower extremity patients.

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Lower extremity (LE) lymphedema is common but with exact prevalence that remains unknown.[1] The morbidity of lymphedema is considerable. Most physicians focus on reducing limb swelling, because the underlying disease is generally not amenable to cure.[2]

Current strategies to improve lymphedema outcomes use methods to increase lymph transport from the limb. The standard of care, referred to as "complete decongestive therapy" (CDT), includes skin care, manual lymphatic drainage (MLD), compression bandaging, compression garments, and selected use of pneumatic compression devices (PCDs).[2–4] The optimal strategy has not been defined from randomized trials but rather from case series and approaches that apply simpler to more stringent compressive strategies. Although robust comparative effectiveness data are lacking, CDT is widely considered to represent the standard of care.[2]

PCDs are frequently used to treat chronic lymphedema. Postulated mechanisms of PCD efficacy include simulating the calf muscle pump, decreased capillary filtration, and reduced venous reflux.[5] Use of PCDs is attractive because it allows patients to continue therapy at home, outside the clinic or hospital setting. Although PCD therapy requires the

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initial cost of purchase, clinical efficacy may result in long-term reductions in use of healthcare services. The majority of publications on PCD efficacy have evaluated device impact in individuals with upper extremity (UE) breast cancer-related lymphedema (BCRL).[5–16] The evidence base for patients with LE lymphedema is limited by a paucity of published data.

Commercially available PCDs include simple single chamber devices providing non-calibrated, non-gradient static compression to the entire limb. PCDs within the next category have multiple chambers (typically 3–10) that provide sequential treatment; may or may not provide gradient pressure; and provide limited adjustability. The advanced PCDs (APCDs) include "new generation" technology that provides calibrated, gradient sequential inflation with additional features enabling custom treatment to address individual patient needs. Some newer devices include garments that treat the core body areas (abdomen and/or chest), and the pressure profiles and treatment areas can be easily adjusted. Most PCDs were designed to impact the venous system and therefore incorporate treatment pressures and sequencing intended to mobilize fluid into the limb vasculature. These devices can best be described as applying a "squeeze and hold" treatment. Some newer APCDs have been designed to specifically impact the lymphatic system, utilizing lower pressure profiles and treatment sequences intended to simulate manual lymphatic treatment techniques.[17]

The APCD utilized in the current study is the Flexitouch system (Tactile Systems Technology, Inc., Minneapolis, MN). This APCD was designed to impact the lymphatic system and mimic MLD by utilizing brief applications of dynamic pressure to apply a gentle stretch against the skin to stimulate lymphatic capillaries. The device is intended for home use during the self-management phase of CDT. Near infrared-imaging has shown systemic stimulation of the lymphatic system, with increased lymphatic propulsion rates.[18] The programmable controller, which offers several treatment programs to address LE swelling, produces a gentle, wave-like application of pressure as the chambers sequentially inflate and deflate. This dynamic pressure is designed to move stagnant lymphatic fluid from the distal swollen limb toward the trunk.

LE lymphedema can adversely affect quality of life (QOL).[19] Treatment has traditionally focused on objective outcomes (e.g., limb volume). As all lymphedema treatments mandate significant commitment from patients, it is essential to assess patient-reported outcomes and satisfaction in addition to objective measures.

The primary purpose of this study was to examine the effectiveness of the Flexitouch system APCD on limb volume (LV) reduction in the treatment of LE lymphedema. Secondary objectives were to compare pre- and post-treatment patient-reported outcomes and to examine clinician-reported outcomes after treatment. Sub-analyses identified factors that may predict treatment responders.

We analyzed data from a prospectively collected database of patients who were prescribed this APCD treatment. This analysis evaluated LV, clinician-reported outcomes, and patient-reported parameters. This device outcomes registry was created because of a unique mandate by a subset of third-party payers which requires that certain PCDs be rented initially in order to evaluate effectiveness prior to purchase. The study population comprised patients who participated in this rental-reauthorization process. The data represent "real world" device experience.

METHOD

From January 2009 to May 2012, 290 LE lymphedema patients received the APCD under a "rental-with-reauthorization process" as required by a third-party payer. After a pre-specified rental period, the patient was reassessed by the referring clinician. This process required that both pre- and post-APCD treatment limb measurements be obtained, and key clinical measurements (e.g., skin changes and function) be reported to the third-party payer. To be considered for this program, patient's stage of lymphedema had to be at least Stage II based on payer criteria. To meet the study entrance criteria, the patients were required to have a signed consent authorizing their data to be used for research purposes, pre- and post-treatment limb measurements and a completed clinical assessment. Ninety-four patients were excluded because of non-provision of research consent ($n = 34$) or missing data ($n = 60$). One-hundred and ninety-six patients met the entrance criteria and were included. The Western Institutional Review Board approved this study (No.1133766).

The follow-up clinical assessment was completed approximately 60 ± 27 days (range 17–242; median 55.5) after the baseline measurements and initial APCD treatment. Chart reviews were completed by an independent research contractor. Data included diagnosis, gender, age, weight, pre- and post-treatment circumferential limb measurements, pre- and post-treatment patient survey responses and post-treatment clinical assessment data. Patient diagnoses were provided by the prescribing physician.

Data were provided by the treating clinicians via a standardized clinical assessment form. The form included assessment of fibrosis/skin hardening, ability to perform activities of daily living (ADLs) and active range of motion (AROM). Although these were experienced lymphedema clinicians, they were provided an illustrated and detailed "Measurement Guide" for obtaining consistently derived circumferential limb measurements. Clinicians measured the limb with the patient standing and bearing weight. The leg inseam was measured from the bottom of the heel to the groin. The lower circumference was recorded at the ankle and then at 10 cm increments from the ankle up to the groin. Utilizing these measurements, LVs were calculated using the formula for a truncated cone, $V = h(C^2 + Cc + c^2)/12(\pi)$, where $V =$ the volume of the segment of the limb, C and c are the circumference at each end, and h is the distance between segments (10 cm).[20]

Upon receipt of the APCD, patients received in-home training on device operation and prescribed treatment protocol. Patients were advised to remove all static compression garments, inelastic bandages and/or wraps prior to device garment application for APCD treatment. Patients were further advised to reapply their daily garments/wraps after APCD treatment. Patients were directed to lie supine during treatment.

The pre- and post-treatment patient survey to evaluate patient-reported effectiveness and satisfaction of the APCD treatment consisted of four questions utilizing a Likert-type scale.

Statistical methods

Analyses were performed on the full cohort of patients and sub-analyses on unilateral and bilateral lymphedema patients. Additional analyses were performed on sub-groups of subjects by lymphedema type.

Continuous variables are described using sample size, mean, and standard deviation. A two-sided p value of $\leq .05$ was used to determine statistical significance for the rejection of the null hypothesis.

For LV change (LVC), a paired t-test was used to compare the mean difference between baseline and post-treatment LVs. Bilateral subjects were analyzed two ways: "Per Limb" (each limb reported separately) and "Per Subject" (using the limb with the greater baseline LV).

For LVC from baseline analyses comparing the effect of treatment between groups, an analysis of covariance (ANCOVA) was used, where the response variable is post-treatment LV and the independent variables are baseline LV and group. An assessment was made of any interaction between group and baseline LV. If the p value for the interaction term in the ANCOVA was above .1, the interaction term was removed from the analysis.

The relationship between body mass index (BMI) and age with LVC was evaluated using linear regression, with LVC as the response variable, using a second degree polynomial fit on BMI and age, as the independent variables, to allow for quadratic (curvilinear) relationships to be explored.

Table 1. Baseline demographics and clinical characteristics.

		Total	Bilateral	Unilateral
Gender	Female	131/196	92/136	39/60
	%	66.8	67.6	65.0
	Male	65/196	44/136	21/60
	%	33.2	32.4	35.0
Age	*N*	196	136	60
	Mean ± SD	55.8 ± 13.3	55.9 ± 13.6	55.6 ± 12.6
	Min, Max	14.5, 86.0	14.5, 86.0	17.2, 83.5
BMI[a] (M^2)	*N*	191	133	58
	Mean ± SD	38.2 ± 13.2	40.9 ± 13.7	31.9 ± 9.3
	Min, Max	18.9, 78.7	18.9, 78.7	19.1, 64.5
Side treated	Bilateral	136/196	136/136	0/60
	%	69.4	100.0	0.0
	Left	31/196	0/136	31/60
	%	15.8	0.0	51.7
	Right	29/196	0/136	29/60
	%	14.8	0.0	48.3
Type of lymphedema	Primary	41/196	31/136	10/60
	%	20.9	22.8	16.7
	Secondary	155/196	105/136	50/60
	%	79.1	77.2	83.3
Previous infections	Yes	75/191	55/132	20/59
	%	39.3	41.7	33.8
	No	116/191	77/132	39/59
	%	60.7	58.3	66.1
Previous PCD treatment	Yes	46/195	30/135	16/60
	%	23.6	22.2	26.7
	No	149/195	105/135	44/60
	%	76.4	77.8	73.3
Duration of diagnosis	>5 years	51/171	44/121	7/50
	%	29.8	36.4	14.0
	2–5 years	31/171	17/121	14/50
	%	18.1	14.0	28.0
	6 months to 2 years	39/171	23/121	16/50
	%	22.8	19.0	32.0
	<6 months	50/171	37/121	13/50
	%	29.2	30.6	26.0

[a] $p < .0001$.

Table 2. Treatment program and frequency.

Treatment program and duration (min)	Bilateral $n = 136$	Unilateral $n = 60$
L1: Full leg and core (trunk) (60)	126	55
L1 + supplement program[a] (60 + 15 to 45)	8	4
L3: Trunk and thigh (30)	2	0
L5: Calf and foot (30)	1	1
Treatment frequency		
QD alternating limbs	79	—
QD both limbs	57	—
QD	—	56
BID	—	4

L1, L3 and L5 correspond to the controller setting on the APCD for the particular treatment program prescribed.

[a] Supplemental programs range in duration from 15 to 45 min each, and are designed to provide focused treatment to a particular body area/region.

Paired comparisons of subject survey responses at baseline and post-treatment were made using Stuart-Maxwell Marginal Homogeneity Tests and Wilcoxon Signed Rank Tests, the latter using numeric rank transformations of the ordinal survey responses. These analyses were performed on subjects responding to both baseline and post-treatment surveys.

No imputation of missing data was performed and individual analyses were only performed on subjects having required data reported for that particular analysis. All analyses were performed using R Version 2.15.0 or greater (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

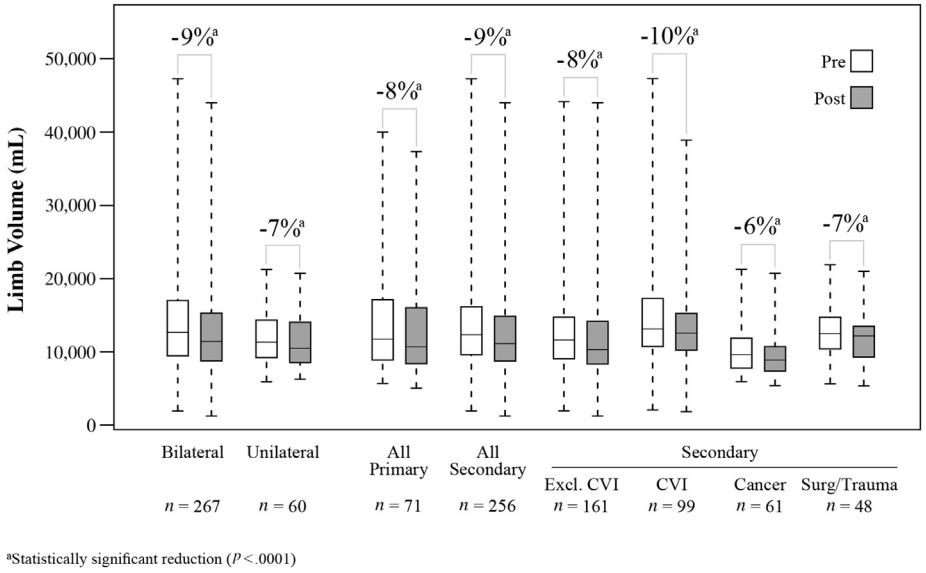
Baseline characteristics are reported in Table 1. The cohort was characterized by more female patients (68%) and individuals with secondary lymphedema accounted for nearly 80% of the study population. The most frequently documented secondary causes of lymphedema were CVI (53), cancer (47), surgery (non-cancer)/trauma (29), infections (14), and other poorly defined etiologies (12).

The prescribed APCD treatment programs and frequency of treatment are presented in Table 2.

LV changes from baseline to post-treatment are illustrated in the boxplot displayed in Fig. 1. Overall, the study population demonstrated a mean LV reduction of 8% or 1,149.7 mL (range 12,411.1 to +3,084.4) ($p = <.0001$.). Baseline LV was a strong predictor of the beneficial response ($p < .0001$), as patients with larger baseline LV had greater LV reduction. Bilateral patients experienced a greater reduction than unilateral patients (representing 9% and 7% reductions, respectively). However, this difference was not significant after adjusting for baseline LV.

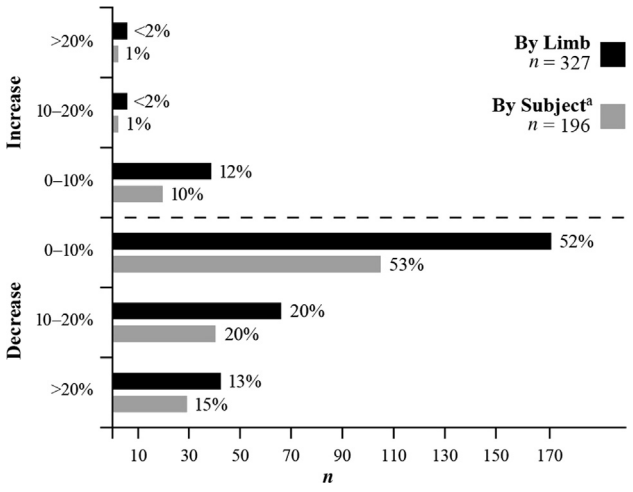
Based on the "per subject" analysis, almost 90% (88%; $n = 173$) of patients demonstrated an LV reduction in response to treatment and 35% demonstrated a substantial reduction >10% (Fig. 2). Based on the "per limb" approach, the response distribution was similar (85%; 33%) (Fig. 2). A minority of patients ($n = 23$ or 12%) experienced an increase in LV. Four patients experienced a LV increase >10%, and, of these, two were non-compliant with PCD treatment. One patient with a >20% LV increase had a long-standing wound that reduced in size during PCD treatment.

There was no significant difference in LV reduction for bilateral patients treated twice daily versus those treated once daily on alternating limbs (8.5% vs. 8.4%, $p = .93$).



[a]Statistically significant reduction ($P < .0001$)

Figure 1. Boxplots for multiple patient subsets, displaying paired pre-treatment versus post-treatment limb volume (LV). The mid-box line represents the median value (50th percentile), and the bottom and top of the boxes represent the 25th and 75th percentiles. The whiskers represent the observed group range. All within subset paired comparisons are $p < .0001$. Bilateral patients achieved a larger reduction in LV than the unilateral patients; however, this difference was not significant after adjustment of baseline LV. The mean reduction in LV (mL) for each subset (left to right) was: 1,225.8, 811.1, 1,150.4, 1,149.5, 1,038.4, 1,368.4, 655.6 and 864.8, respectively.



[a]For bilateral subjects, the leg with the greater pre-treatment limb volume was used as the index limb, unless data was only available for one of the two legs (n=4).

Figure 2. Percent change in limb volume (LV) from baseline.

Patients with CVI demonstrated the greatest reduction of 10%, but the differences among patients with different diagnoses was not significant.

Patient factors such as age and BMI were also analyzed for an association with response to APCD treatment (Fig. 3). Larger BMI was associated with greater reduction in LV ($p < .0001$). There was a trend for older patients to have lesser reduction in LV, but this was not statistically significant ($p = .29$). Similarly, patients with larger baseline LV had greater reduction. Additional testing with a single independent variable (either BMI or baseline LV, both again quadratic) was also done. The R^2 for each model (BMI = .0636, baseline LV = .1820) suggested that while neither variable accounted for the majority of the variation in LV reduction, baseline LV was a more important predictor of response.

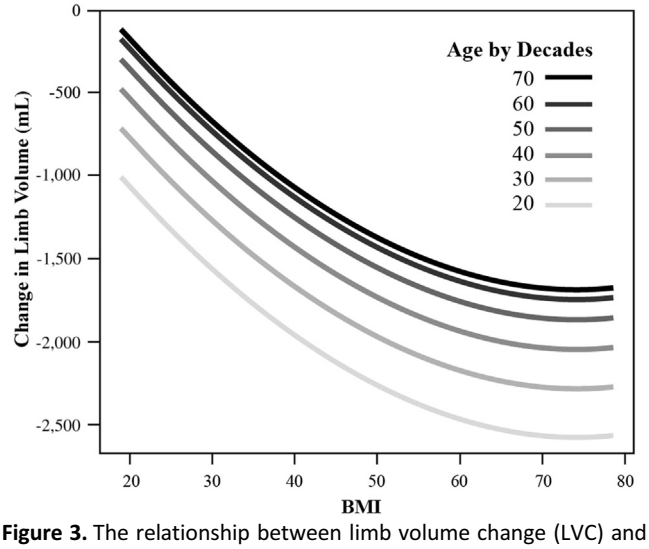


Figure 3. The relationship between limb volume change (LVC) and body mass index (BMI). This figure demonstrates that as BMI increases, limb volume (LV) reduction with advanced pneumatic compression device (APCD) treatment also increases significantly. As age increases, LVC tends to decline (p = NS).

Post treatment patient survey and satisfaction

The post treatment survey, consisting of four questions utilizing a five-point Likert scale, was completed by 98 patients yielding a 50% completion rate. Patients demonstrated consistent improvement in response to treatment, with three of four questions showing a statistically significant positive category shift (Fig. 4). Patients reported an increased ability to control lymphedema through APCD treatment at home. Patients also reported an increased ability to perform ADLs and a reduction in the frequency of pain with ADLs. Sixty-six percent of survey responders indicated they were "Very Satisfied" overall with APCD treatment, and another 30% ($n = 29$) indicated they were "Satisfied".

To address the possibility of a survey response bias, a responder analysis was completed. LVC for patients that returned the survey (response) was compared with that for patients who did not return the survey (non-response). The response group had a reduction of 8% or 1,049.7 mL (range −10,433.5 to +2,328.4), whereas the non-response group had a reduction of 9% or 1,242.1 mL (range −12,411.1 to +3,084.4). Thus, patients with large LV reduction were not over-represented among the survey responders. Other patient characteristics (age, gender) were also similar between the two groups.

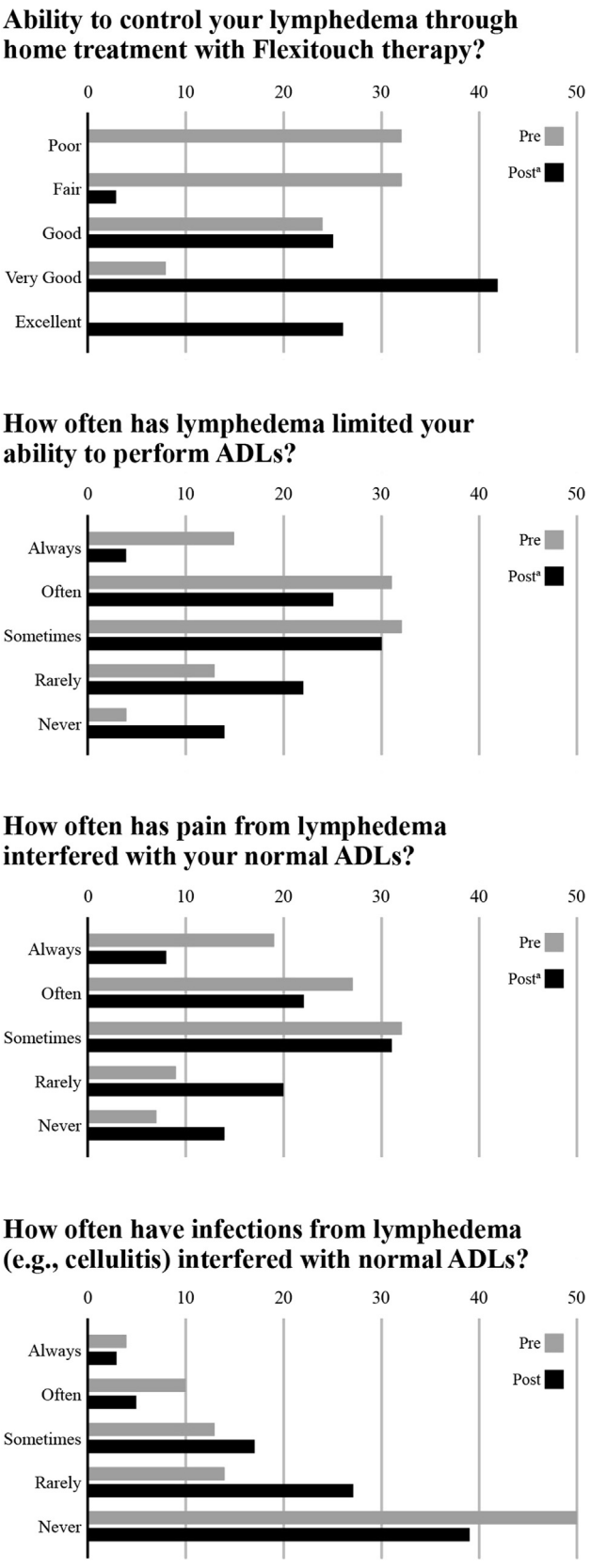
Clinician assessment

In 86% ($n = 168$) of the patients, a reduction in skin hardening or fibrosis was reported based on manual assessment of skin pliability and tethering. Based on clinical observation of function, nearly all (85%; $n = 165$) patients demonstrated an increased ability to perform ADLs; a high fraction (77%, $n = 149$) also demonstrated increased AROM.

Adverse events. Four adverse events (AEs) were recorded for these subjects. Two events were likely related to device treatment: one patient experienced muscle cramps and a second reported increased limb erythema. The other two events were unlikely to be related to device treatment and included a non-specific allergic reaction and increased fatigue. All AEs resolved, and patients continued to use the APCD.

DISCUSSION

Prevalence and impact of LE lymphedema are high, but large studies of the response of this condition to compressive therapies are few. The current study represents, to our knowledge, the largest study of PCD outcomes in LE patients. These data demonstrate that APCD use is associated with a mean LV reduction of 1,149.7 mL or 8%, and this reduction was consistently achieved across the treatment cohort (only 12% of patients did not demonstrate



[a]Statistically significant difference ($p < .0001$)

Figure 4. Pre- and post-advanced pneumatic compression device (APCD) treatment patient survey questions and results.

LV reduction). This reduction was associated with improvement in QOL and no significant adverse effects.

The magnitude of response observed in this study cannot be readily compared with previous LE lymphedema studies, because these older studies reported limb diameters at various anatomic landmarks, making it difficult to calculate LVs.[7,8,13] LV reduction data are more readily available for UE patients. In a systematic review, Moseley[21] found average LV reduction of 26% across several studies after PCD therapy; however, because of large differences in muscle and bone mass, the fractional LV reduction that can be achieved is likely to be different for arms and legs.

Objective evaluation of PCDs has been suboptimal, contributing to an environment in which the opinion of experienced clinicians is substituted for high-quality data. Most studies have examined UE BCRL. One randomized post-mastectomy study of 80 patients showed no benefit from PCD treatment.[11] Another randomized study of 27 BCRL patients found that PCD therapy had benefit when used adjunctively to CDT.[10] A pilot study of BCRL patients found that PCD treatment utilizing the same device as the current study was more effective in reducing arm volume and patient weight than self-administered MLD.[14] In a single-arm study of 25 patients (7 UE; 18 LE), Richmand reported significant LV reduction with short-term, in-hospital PCD use.[13] The same group studied 49 patients over a longer term (mean 25 months) and found that 36 patients maintained either full- or partial-response.[8]

Evaluation of published data is also challenged by the high inter-study variability of types of PCDs. Early single-chambered sleeves with simple controllers have been largely replaced by more sophisticated multi-chamber devices, which have varying degrees of programmability for the amount and timing of pressure in each chamber. Most PCDs employ a simple concept of 'milking' the limb (i.e., they generate higher pressures distally and progressively lower pressures proximally). These devices typically generate relatively high static pressures of 30—60 mmHg in the UE and 80—110 mmHg in the LE.[22,23] The PCD used in this study provides a more complex sequence of dynamic pressurization designed to mimic MLD, including a chamber inflation pattern designed to replicate the "work and release" and "hand-over-hand" manual techniques. It generates a substantially different pressure profile with application of mild, directional and variable pressure followed by an immediate release of pressure.[22] This mechanism is intended to facilitate the collection and re-absorption of lymph fluid, much like MLD. Another feature intended to simulate MLD efficacy is the option to treat the lower abdomen, a component absent from most PCDs.

This study demonstrates that neither age nor etiology of lymphedema was a predictor of treatment-related LV reduction. Larger BMI and larger baseline LV were strong predictors of LV reduction. As one would expect, these two parameters are not independent. However, the impact of an increased baseline LV was stronger than the effect of BMI. Thus, the most severely affected patients with lymphedema can anticipate the best treatment efficacy.

Although LV reduction is an important objective goal of lymphedema therapy, it is also critical that this reduction be associated with improvement in patient-reported outcomes. A small LV reduction can result in a large improvement in function, thus improving QOL.[16] Conversely, patients may remain symptomatic despite experiencing significant reductions in LV. The current study demonstrated a significant positive impact of APCD treatment on function and pain components of QOL, as demonstrated by a category shift in three of the four questions that pertained to control in managing lymphedema at home.

Our study suggests that home treatment with an APCD resulting in a mean LV reduction of 8% provides clinically meaningful impact for the patient. This finding is supported by the work of Cormier and colleagues who concluded that LVC as minimal as 5% had a clinically significant impact on signs and symptoms[23] including tenderness, tightness, heaviness, and pain. The Cormier study included only UE patients, so inferences regarding patients with LE lymphedema are limited. It is possible that a minimal LV reduction for LE patients would provide a large QOL impact, as the legs sustain balance and mobility, facilitating functional independence. Another study found that patients with LE lymphedema had significantly greater improvement in QOL scores compared with UE patients after CDT ($p = .02$).[24] There was no correlation between the magnitude of edema reduction and the post-treatment QOL improvement, indicating that there are other benefits to treatment than LV reduction alone.

The current study also measured clinician assessment of tissue fibrosis, ability to perform ADLs, and AROM. These data showed high rates (77—86%) of favorable responses for these outcomes, suggesting that APCD treatment demonstrated therapeutic value beyond LV reduction.

This study has significant limitations. Although data were collected prospectively, registries can never fully represent the population, including individuals with barriers to care. This registry report also lacks comparative effectiveness data. Other lymphedema treatment components were not standardized. LV measurements were done at variable time points after initiation of therapy (60 ± 28 days). The study did not include every patient who may have been treated with this device, and half of the patients did not give post-treatment responses to the survey. However, as survey responders and non-responders had very similar demographic characteristics and degrees of LV reduction, this bias may be minimal. Despite these limitations, the data reflect a "real world" experience, which showed statistically significant and clinically meaningful response to APCD therapy in a large cohort.

CONCLUSION

The study demonstrates that APCD treatment can reduce LV, improve pain, and enhance ability to complete ADLs. Thus, patients with LE lymphedema enjoyed an improved QOL. Although these data confirm that clinical benefit is consistently achieved in real world settings, additional prospective research would help define predictors of improved treatment success, as well as the health economic impact of such treatment.

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CONFLICT OF INTEREST

Drs. Satish Muluk and Elisa Taffe have no competing interests to declare.

Dr. Alan Hirsch serves as the Chief Medical Officer of Tactile Systems Technology, Inc., which manufactures the treatment device studied in this report. This relationship has been reviewed and managed by the University of Minnesota in accordance with its Conflict of Interest policies.

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