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Review Article

A Review of Pneumatic Compression Therapy in the Treatment of Lymphedema

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Introduction

Lymphedema, a condition which typically affects the extremities, is characterized by accumulation of protein-rich fluid in the soft tissues due to malfunction of the lymphatic system. The normal role of the lymphatic system is to passively convey and actively pump interstitial fluid back into the blood stream. Primary (congenital) lymphedema arises from poorly understood factors, while secondary lymphedema is caused by another known disease. Most often, upper extremity secondary lymphedema is the result of breast cancer, with an incidence of 15-20% among female breast-cancer patients who have undergone a mastectomy or radiation as part of therapy [1]. It has been estimated that primary lymphedema affects 1.15 out of 100,000 children in North America [2].

The treatment of lymphedema is challenging. A mainstay of current therapy is Complete Decongestive Therapy (CDT), which includes the use of compression bandages, skin care, exercise and Manual Lymphatic Drainage (MLD). MLD is a massage conducted by a trained therapist and designed to stimulate lymph flow in the limb. Pneumatic Compression Devices (PCDs) have also been used in the management of lymphedema. PCDs are used to promote lymphatic and venous return from distal parts of the body back to proximal areas. The simplest PCDs have a single sleeve which alternately compresses and decompresses. More complex PCDs have multiple, programmable sleeves. At least one PCD uses a programming algorithm that is designed to mimic MLD [3]. Despite this wide variety of devices, the utility of PCDs has not yet been definitively established.

The primary aim of this review is to evaluate published data regarding the effectiveness of Pneumatic Compression (PC) in treating lymphedema patients. Effectiveness here is defined as an ability to significantly reduce affected limb volume, improve quality of life, and improve clinical outcomes. The secondary aim is to compare PC to other forms of treatment for lymphedema, chiefly CDT.

Methods

Potential articles for this review were first identified using two Boolean search terms (“pneumatic” and “compression” and “lymphedema”; “pump” and “lymphedema”) in both Ovid Medline and Pubmed databases for the years 1990 to 2016. The search was limited to English-language articles. Abstracts obtained through this search were reviewed to identify those articles which (1) were primary studies of human lymphedema (i.e. animal models and reviews were excluded); (2) provided information about the effect of PC on limb volume, quality of life, or clinical outcomes of lymphedema. The final set of articles identified by this process are listed in (Table I). In the analysis below, all reported inter-group differences were found to be statistically significant ($P<0.05$), unless otherwise mentioned.

The Effectiveness of Pneumatic Compression

Limb volume reduction: We identified 13 studies [4-16] which have examined the effect of PC on limb volume for patients suffering from upper or lower extremity lymphedema. Overall, the existing data suggest that PC can significantly reduce limb volume among lymphedema patients. However, this conclusion is not definitive, because the available studies (1) typically have small cohorts or lack a control group and (2) use widely varying methodologies and compression devices.

A study [4] of 80 patients with upper extremity lymphedema found that pneumatic compression causes a significant decrease in an edema index calculated by measuring the difference between the affected limb and normal limb at 7 matching points. These differences were added to calculate the index. Measurements were taken before and after a course of pneumatic compression. The index declined significantly after PC treatment (1.9±3.7 cm, 11.8% of the original value of the index), whereas the decline in the control group was non-significant (0.5±3.3 cm, 3.4%).

Johannson et al [5] studied upper extremity lymphedema patients, measuring both the absolute volume of the affected limb (LV) as well as Edema Volume (EV, measured by examining the difference between the volume of the affected arm to that of the unaffected arm). After PC therapy, Limb Volume (LV) declined by 2.08%, while Edema Volume (EV) dropped by 7%. Another study [6] examined only a single 3-hour session of PC for lower extremity lymphedema and identified reduction ranging from 1.2 to 3.3% in limb circumference, depending on the location of measurement.

Szuba et al [7] reported two studies of upper extremity lymphedema in a single publication. Among new lymphedema patients, two weeks of CDT and PC led to EV reduction of 45.3%. Among a separate group of chronic lymphedema subjects, EV was reduced by 89 ml after 1 month of PC.

Szolnoky et al [8], studying patients with lower extremity lymphedema undergoing CDT and PC, found that LV dropped by 1232 ml, or 8%. Pilch and colleagues studied multiple PC regimens among upper extremity lymphedema patients, finding that the different PC regimens were not significantly different from one another [9]. Across all patients, LV dropped by 240 ml (6.2% from baseline), while EV fell by 36.1% from baseline.

Another study [10] of upper extremity lymphedema patients, using a cumulative circumference index for edema similar to that described above, reported a reduction of 27% following a 4-week course of PC.

Another study examined two different types of PC for the treatment of upper extremity lymphedema. One device was an ‘advanced’, multi-compartment, PC device which was designed to be programmed to mimic MLD (APCD). The other was a ‘standard’, multi-compartment, non-programmable device designed to milk fluid from the extremity by sequential cuff inflation (SPCD). The APCD group experienced a drop in LV of 150 ml (4.8% from baseline) and a drop in EV of 118 ml (21.2%). The SPCD group had a drop in LV of 91 ml (2.9%), but EV increased slightly by 6.3 ml (1.2%).

Gurdal et al, measured LV reduction of 439 ml (12.2% from baseline) among 15 patients treated with a 6-week course of PC. Moattari and colleagues [13]. Studied 42 upper extremity lymphedema patients, measuring both EV and a cumulative circumference index of edema. After a 4-week course of CDT and PC, EV dropped by 30%, and the circumference index fell by 31%.

Another study compared CDT and PC (16 subjects) to CDT alone (15 subjects) for upper extremity lymphedema. The group receiving combined therapy exhibited EV reduction of 340 ml (40.4% from baseline), while the group receiving CDT alone had EV reduction of 150 ml (23.8%). Both changes were significant when compared to baseline EV, but the difference between the two treatment groups was not statistically significant.

A study of 18 patients with unilateral leg lymphedema examined circumference at five levels of the leg [15]. Patients received long-term daily PC therapy at home. The cumulative leg circumference dropped by 9.4cm (4.2% from baseline) at 1 month, 20.4cm (9.1%) at 12 months, and 14.3cm (6.4%) at 24-36 months. After three years, there was no further decrease in limb circumference, but an increase in tissue elasticity was observed (Zaleska).

Muluk and colleagues measured LV before and after therapy with a PC device which mimics MLD. After an average therapy interval of 60 days, LV dropped by 1150ml (8% from baseline).

Although the studies overall demonstrate reduction in limb volume, it is important to note that multiple different types of pumps and methods of application were used, and that the studies typically had a small number of patients.

Quality of life and clinical outcomes: The bulk of lymphedema studies have examined the effect of PC on volume-related parameters, sometimes combined with related extremity parameters such as skin tonicity or range of motion. A few recent studies have looked at Quality-Of-Life (QOL) and clinical outcomes after initiation of PC therapy. It is well established that untreated lymphedema patients have substantial functional impairment [2-16].

In the study by Muluk et al [16] mentioned above, QOL questionnaires were administered before and after PC therapy. These patient-reported data demonstrated a significant increase in ability to control lymphedema after PCD initiation, an increase in function, and a reduction in the occurrence of pain. Two-thirds of patients reported that they were “very satisfied” with PCD therapy. However, the study had no control group.

Another study [17] was a retrospective claims analysis of 1,065 cancer-related lymphedema patients. Subjects were included only if they had 12 months of continuous insurance coverage prior to PC receipt, as well as a 12-month follow-up period. Usage of medical services after PC initiation was compared to that before PC initiation. PC usage was associated with decreased rates of hospitalization (45% to 32%), outpatient hospital visits (95% to 90%), physical therapy use (50% to 41%), and receiving a diagnosis of cellulitis (28% to 22%). Total healthcare costs also declined (-$11,833 per patient).

A similar analysis [18] was conducted after using claims data to identify 718 cancer and non-cancer related lymphedema patients who received an advanced PCD designed to simulate MLD. The authors observed a reduction in outpatient visits for both cancer patients (58.6% to 41.4%) and non-cancer patients (52.6% to 31.4%). Additionally, there was a reduction in related costs per cancer patient (37%) and non-cancer patient (36%). Reduction in cellulitis episodes was similar in both cohorts, 21.1% to 4.5% in cancer patients and 28.2% to 7.3% in non-cancer patients.

These claims-based studies offer interesting indirect data, but the results cannot be considered definitive without direct study of lymphedema patients.

Pneumatic Compression Compared to Other Forms of Treatment

Limb volume reduction: Despite the fact that PC appears to reduce limb volume, it is unclear whether the effect of PC is superior or additive to the effect of other therapies.

In the Dini study [4] mentioned previously, the authors used an arbitrary threshold of 25% reduction in the edema index to determine that the limb size reduction in the PC group was clinically non-different from the control group. In the Gurdal study, the group receiving PC and self-lymphatic drainage was found to have statistically similar upper limb volume reduction as the group that underwent CDT [12].

Two studies [8,14] reported that PC patients had similar volume reduction as CDT patients in both upper [14] and lower [8] extremity lymphedema. In the both studies, the addition of PC to CDT led to a greater volume reduction than with CDT alone, but the difference was not statistically significant. This may have been due to small sample size (Type II error).

Kozanoglu and colleagues [10] measured similar short-term volume reductions between PC and low-level laser therapy groups. Laser therapy, which has been theorized to increase lymph flow, was administered using a Ga-As 904 nm laser device. After the initial therapy, which lasted for 4 weeks, volume reduction persisted for 12 months after laser therapy but not after PC.

A single study found that the decrease in limb volume from PC was significantly less than that from MLD [5].

A single publication [7] found that combined CDT and PC was significantly better than CDT alone in the treatment of patients with new-onset upper extremity lymphedema. The CDT-only group had 26% mean EV reduction whereas the combined therapy group experienced mean EV reduction of 45.3%. The same paper analyzed chronic upper extremity lymphedema patients using a randomized crossover study design which compared CDT to PC. Patients receiving PC (as the first or second modality) experienced average EV reduction of 89ml, while CDT patients exhibited an average increase of 33ml.

Because of widely ranging methodologies and small numbers of subjects, the studies, even when analyzed as a group, fail to definitively demonstrate whether PCD therapy is superior to and/or a valuable adjunct to CDT.

Quality of life and clinical outcomes: Only three small studies have attempted to compare QOL and clinical outcomes among patients treated with PC and alternative/adjunctive modalities. All found that other treatments were more beneficial than PC.

In one study, emotional functioning, fatigue, and pain improved in both the PC group and the CDT group, but global health status, functional and cognitive functioning scores only improved in the CDT group [12]. Similarly, another study found that tension and heaviness only improved in the MLD group [5].

Both low-level-laser and PC-treated patients had pain reduction in the immediate post-treatment phase [10]. However, at follow-up ranging up to 12 months after the treatment, only the low-level laser therapy patients had continued significant pain reduction.

Because so few studies have examined whether QOL and other clinical outcomes are better with PCD than alternative therapies, one cannot draw any firm conclusions about this important question.

[Table I] summarizes the various articles discussed in this review.

Discussion

A significant body of literature supports the conclusion that PC leads to reduction in limb volume among patients with both upper and lower extremity lymphedema. As shown in [Table I] absolute limb volumes have been shown to be reduced from 2% to 12%. Edema volume, measured by comparison to the unaffected extremity, has been shown to decline from 20 to 40%. These findings must be interpreted with caution, because the available studies generally have small subject numbers and in some cases lack a control group. In addition, the studies have used widely varying methodologies. Some of them have analyzed PC as standalone therapy, whereas others have studied PC as adjunctive therapy to CDT. There is also a wide range of measured endpoints (e.g. limb volume, edema volume, cumulative circumference differential).

Another major impediment to interpreting existing studies is that PCDs come in many different varieties, including single-compartment devices; multi-compartment devices with and without sequential inflation/deflation (i.e. 'milking') capability; and advanced devices having algorithms designed to mimic MLD [3]. Additionally, as shown in [Table 1] each device can be used with different pressure and duration regimens. Thus, it is difficult to draw conclusions across multiple studies.

A single study [11] found that APCD therapy was superior to standard PCD therapy in the care of upper extremity lymphedema patients. However, in general, the available data do not allow us to compare one pump type to another or one PCD regimen to another.

A related question to the one about volume reduction is the functional impact of PCD. Several of the reviewed studies [5-13] demonstrated improvements in functional parameters, such as pain, skin tonicity and range of motion. However, the small sample sizes and varying endpoints make it impossible to draw any definite conclusions. In particular, there are insufficient data to determine how much volume reduction is necessary to improve patient function. A single study [16] used a standardize questionnaire to measure QOL improvements among PCD-treated patients.

PCD therapy is noninvasive, but one cannot assume that it is benign. For example, one study noted that PC can increase truncal and genital lymphedema as fluid is pushed proximally [19]. However such adverse effects were not confirmed by the studies reviewed for the current paper.

Ideally, an effective therapy for lymphedema would lead to reduced healthcare utilization, decreased cost and lower rates of cellulitis. These desirable endpoints have not been directly demonstrated, but they have been indirectly demonstrated in two large retrospective analyses of claims data. In both papers [17], the authors found that patients used significantly fewer healthcare resources and had fewer diagnoses of cellulitis in the year following PCD acquisition. These tantalizing findings will need to be validated by direct study of patients who receive PCDs.

Complete Decongestive Therapy (CDT) of which MLD is a central component has become widely accepted as the mainstay of therapy for lymphedema. Several authors noted that PC has potential benefits because it is easier for patients to use on their own at home as compared to MLD, which requires trained therapists. In-home use may increase possibilities for more wide-spread applicability because therapists are not needed to administer the treatment. This potentially makes PC a more cost effective option as well [8-15] Thus, it would be useful to know whether PCD therapy can effectively replace and/or supplement CDT. The available studies do not offer any definitive answers to these questions, but overall, the data indicate that PCD should be considered as a viable option when patients cannot receive or fail CDT.

Table 1: Summary of previous articles that have studied pneumatic compression.

First author	Year	Extremity	Authors' Conclusions	N	Study type	PCD regimen	PCD type	LV reduction	EV reduction	Circumference reduction*
Dini	1998	Upper	PCD is no better than no treatment	80 (40 per group)	RCT (PC vs no Rx)	60 mm Hg; five 2-hour sessions per week for two weeks, repeated after a five-week interval	Single compartment			PC: 1.9 cm (11.8%) . Control: 0.5 cm (3.4%)
Johansson	1998	Upper	MLD is better than PC at reducing volume	24 (12 per group)	RCT (MLD vs PC)	40-60 mm Hg 2 hours daily for 2 weeks	Multi-compartment sequential	PC: 57 ml (2.08%); MLD: 94 ml (3.18%) MLD	PC: 28 ml (7%); MLD: 75 ml (15%)	
Miranda	2001	Lower	PC reduced mainly ankle and lower leg circumeference	11	Single arm	Single session 3 hours	not specified			1.2-3.3 % (depending on location of measurement)
Szuba	2002	Upper	Addition of PC to CDT significantly improved volume reduction among new-onset lymphedema patients	23 (12 CDT only; 13 CDT+PC)	RCT (CDT vs CDT+PC)	30 min daily after 30-min MLD for 2 weeks. 40-50 mm Hg	Multi-compartment sequential		CDT+PC: 45.3%; CDT only: 26%	
Szuba	2002	Upper	PC was more effective than CDT in reducing volume for chronic lymphedema patients	25 (13 PC first; 12 CDT first)	RCT crossover (MLD only vs MLD+PC)	60 min daily for 1 month. 40-50 mm Hg	Multi-compartment sequential		CDT: 89 ml; MLD: 32.7 ml **increase**	
Szolnoky	2008	Lower	No difference between PC and CDP	24 (11 CDT; 13 CDT+PC)	RCT (CDT vs CDT+PC)	30 min pump after 30 min MLD for 5 days. 30 mm Hg	Multi-compartment sequential	CDT+PC: 1232 ml (8.0%); CDT only: 936 ml (5.2%)		
Pilch	2009		PC reduces limb volume	57	RCT (4 different pump	25 one-hour sessions over 5 weeks. 50-	1-chamber or 3-chamber	All groups: 240 ml	All groups: 36%	
			regardless regardless of pump algorithm		algorithms)	70 mm Hg	sequential; 1:1 and 3:1 pump:rest times.	-6.20%		
Kozanoglu	2009	Upper	PC is similar to low-level laser initially, but laser is better in long-run	47 (23 PC; 24 Laser)	RCT (PC vs Laser)	2 hours daily for 4 weeks. 60 mm Hg	Single compartment			PC: 27.0%; Laser: 33.9%
Fife	2012	Upper	APCD is more effective than SPCD in reducing limb volume	36 (18 per group)	RCT (APCD vs SPCD)	1 hour daily for 12 weeks. UE01 for APCD, 30 mm Hg for SPCD	APCD simulating MLD vs Multi-compartment sequential	APCD: 150 ml (4.8%); SPCD: 91 ml (2.9%)	APCD: 118 ml (21.2%); SPCD: 6.3 ml (1.2%) increase	
Gurdal	2012	Upper	PC is no different than CDT	30 (15 per group)	RCT (CDT vs PC)	Every other day for 6 weeks; 25 mm Hg	Multi-compartment sequential	PC: 439 ml (12.2%); CDT: 529 ml (14.9%)		

Moattari	2012	Upper	Combined CDT and PC reduced limb volume. This benefit was maintained after PC was discontinued and only CDT continued.	42	Single-arm sequential therapies (CDT+PC, then CDT only)	3 sessions weekly for 4 weeks, 15 minutes PC per session after MLD	not specified		CDT+PC phase: 30%; CDT phase: 26% (both relative to pre-treatment baseline)	CDT+PC phase: 31%; CDT phase: 36%
Uzkeser	2013	Upper	PC did not add any benefit over CDT alone	15 MLD only; 16 MLD+PC	RCT (CDT+PC vs PC)	5 times weekly for 3 weeks, 45-min sessions. 40 mm Hg.	Multi-compartment sequential		CDT+PC: 340 ml (40.4 %); CDT only: 150 ml (23.8%)	
Zaleska	2014	Lower	PC reduced limb size over long followup	18	Single arm	Daily for 3 years, 50-125 mm Hg.	Multi-compartment sequential			9.4 cm (4.2%) at 1 month; 20.4 cm (9.1%) at 12 months; 14.3 cm (6.4%) at 24-36 months
Muluk	2014	Lower	APCD reduced limb volume and improved QOL	196	Single arm	1 hour daily for mean of 60 days	APCD simulating MLD	1150 ml (8%)		
Brayton	2014	Both	PCD use led to reduced use of healthcare services and lower incidence of cellulitis	1065	Retrospective (claims database)	n/a	All types			
Karaca	2015	Both	APCD usage led to reduced use of healthcare services and reduced incidence of cellulitis	718	Retrospective (claims database)	n/a	APCD simulating MLD			

PC:pneumatic compression. PCD: pneumatic compression device. LV: Limb volume. EV: Edema volume (calculated by comparison to unaffected extremity). CDT: complete decongestive therapy. MLD: Manual lymphatic drainage. APCD/SPCD: Advanced/Standard PCD (see text for details). All volume and circumference reductions are relative to baseline measured prior to any treatment.

*Refers to sum of circumference measurements of affected extremity *minus* circumferences of unaffected extremity at matching locations (except for Miranda paper, which measured only circumferences of the affected leg)

Summary

This review found significant evidence that PCD therapy reduces limb volume for both upper and lower extremity lymphedema. However any conclusions about the functional and QOL benefits of PCD are tenuous at this time. We also identified indirect evidence that PCD treatment leads to reduced healthcare resource utilization and episodes of cellulitis. Finally it is uncertain whether PCD therapy can effectively replace and/or supplement CDT, but there are enough data to support the idea that PCD should be considered as a viable option when patients cannot receive or fail CDT. Because of variable methodologies and endpoints among existing studies, there remains a great need for high quality studies of PCD therapy. These studies should include (1) comparative analysis of different types of pumps; (2) validated endpoints, including both limb volume and QOL measurements; (3) comparison to non-PCD modalities such as MLD; and (4) larger numbers of subjects.

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