Lymphology 51 (2018) 148-159

ADJUNCTIVE ROLE OF MANUAL LYMPH DRAINAGE IN THE HEALING OF VENOUS ULCERS: A COMPARATIVE PILOT STUDY

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ABSTRACT

Compression therapy plays a pivotal role in the treatment of venous leg ulcers and clinical observations include lymph stasis as contributing to the maintenance of chronic wounds. This finding raises the question whether further improvement in lymph circulation with manual lymph drainage (MLD) as a part of complex decongestive physiotherapy (CDP) can improve ulcer healing. We examined whether CDP improves healing of venous leg ulcers and compared the efficacy of CDP with that of multilayered compression with short-stretch bandages. Eight patients (mean age: 64.8 years, mean ulcer area: 23.07 cm^2, duration of ulcers: 25.37 months) were treated with a 5-day-course of CDP and 9 patients (mean age: 70.77 years, mean ulcer area: 21.47 cm^2, duration of ulcers: 15.8 months) were included in a 10-day-course of CDP. Control goup consisted of 9 patients (mean age: 56.33 years, mean ulcer area: 13.87 cm^2, duration of ulcers: 6.11 months) receiving multilayered compression. Wound surface measurement was carried out on days 5 and 10 and ulcer area reduction rate was calculated as area (initial)-area (final)/time unit. There was no statistical difference between the 5-day-course of CDP and compression of the same duration regarding ulcer healing (t=-1.62, df=15, p= 0.125). A 10-day-course of CDP significantly increased ulcer healing compared to compression of the same duration (t=-2.42, df=16, p= 0.039). Our preliminary results suggest that MLD as a part of CDP supports healing of venous leg ulcers.

Keywords: manual lymph drainage, venous leg ulcer, compression, ulcer size, lymph stasis

The most advanced form of chronic venous insufficiency is persistence of chronic wounds of the lower extremities. This complication poses a common problem in medical practice and is one of the leading morbidities in the older population (1). Nearly 80% of all leg ulcers are of venous origin. Increased ambulatory venous pressure in the distal leg veins is transmitted to the capillary network, causing severe microangiopathy of blood and lymph capillaries (2-10). Capillary stasis damages the endothelial cell layer, and increasing fluid extravasation and capillary vessel-wall thickening can be observed. Uneven endothelial surface and protrusion of endothelial cells cause partial capillary occlusion that contributes to the formation of microthrombi. Microangiopathy is associated with the migration and trapping of white blood cells causing

sustained release of cytokines, chemotactic factors, and proteolytic enzymes. This coexistence of phenomenons can also lead to severe inflammatory changes. Venous hypertension results in high filtration pressure that appears in the tissues as increased lymphatic waterload since the lymphatics play a role as safety valves. When lymphatic transport capacity is exceeded by the waterload, a state of low-protein edema occurs because of the dynamic failure. Longstanding lymphatic hypertension causes infiltration of lymph into the perilymphatic tissue (interstitium), causing fibrosclerosis and lymphangitis. Protein permeability increases and lymphatic vessel damage follows. Electron microscopic examination shows the lack of open junctions and harboring, thin anchoring filaments of lymph vessels (10). Formation of dense bundles of collagen and elastic fibers around lymph vessels further decreases interstitial fluid exchange. Beyond chronic venous congestion, lymphatic insufficiency (high-protein edema) then becomes a hallmark of ulceration. These alterations of blood and lymph vessels result in tissue hypoxia and local edema, ultimately leading to trophic skin lesions. Capillary microscopic studies have demonstrated granulation tissue capillaries embedded in heavy microedema.

Beyond the previously described pathological changes, the maintenance of chronic wounds is also partially based on the imbalance between protelytic enzymes and growth factors (11-16). The main source of proteases are granulocytes and macrophages. They degrade useful factors that promote ulcer healing and also damage capillaries. Certain bacterial strains, especially *Pseudomonas*, also produce a large quantity of peptidases (17). In chronic wounds, altered in blood and lymph microcirculation is associated with impaired immune cell traffic that sustains the production of proteases. Bacterial colonization or continuous superinfection also attracts white blood cells resulting in higher proteolytic enzyme production.

In accordance with published research, the role of lymphatic insufficiency is rather underestimated in venous leg ulcers (3). Lymphoscintigraphy is a useful tool to detect abnormalities lymphatic macrocirculation and to partially that of microcirculation (18). One lymphoscintigraphy study revealed that legs with the most severe form of venous insufficiency are always accompanied by lymphatic involvement. Our observations are in accordance with these previous results in longstanding venous insufficiency with clinical manifestations of lymphedema and dermatoliposclerosis. In earlier stages, the existence of leg ulcer is associated with accelerated lymph flow in the affected leg. This finding might be explained by higher venous afterload and subsequent lymphatic input, active inflammation of the wound, and a compensatory mechanism (19). Lymphatics within the ulcer base and periulcer region are insufficient and therefore deep collectors must increase their capacities. Morphological studies provide a similar result when biopsy specimen were obtained from wound and periwound area (20) as well as near infrared fluorescence lymphatic imaging using indocyanine green contrast medium (21).

Leg ulcer treatment should primarily focus on the reversal of causes with conservative treatment comprising the improvement of venous and lymphatic impairment. The surgical approach has also proven to be successful in healing of ulcers due to primary venous insufficiency (22).

Various forms of compression therapy have proved to be efficient in treating chronic venous insufficiency-based wounds (23). Bandaging can be applied with short or long stretch materials with short stretch material exerting high working and low resting pressure to the leg (24). Activation of the calf muscle pump under short stretch compression induces a so called "self-massage" to both superficial and deep venous system together with lymphatic network enhancing blood and lymph flow and decreasing ambulatory venous pressure and lymphatic overload (25,26). Long-stretch bandaging has a higher effectiveness at rest and is suitable for individuals with impaired mobility. Generally, compression stockings (compression class 2) have a lower working and higher resting pressure compared to short-stretch bandages although class 3 stockings share some of the

similarities with the behavior of short-stretch bandages (27).

Compression therapy can be adjusted with physiotherapy (28,29). The German Society for Phlebology Guideline recommends manual lymph drainage and intermittent pneumatic compression as optional treatments for various degrees of venous insufficiency (30). Complex decongestive physiotherapy (CDP) for lower extremities is based on manual lymph drainage (MLD), multilayered compression with short-stretch bandages, regular walk-trainings, and meticulous skin care (29). Manual lymph drainage (MLD) is a gentle massage technique that is a standard and effective therapeutical tool in various forms of primary and secondary lymphedemas. Multilayered compression bandaging plays an important role in the further reduction of leg volume by enhancing the continuous pumping mechanism using the active involvement of muscle pumps. Intermittent pneumatic compression (IPC) might be a supplementary treatment to MLD, that primarily improves venous flow (31-40). The intensive phase of the treatment is followed by the maintenance phase consisting of the daily use of standard or individually sized compression garments (29).

In various studies, intermittent pneumatic compression appeared to be a useful adjunctive method to improve ulcer healing when it is combined with compression (34-38). However, there is no current evidence on the efficacy of MLD and CDP in venous origin leg ulcer therapy. Therefore we aimed to measure the efficacy of CDP and its component MLD in the healing of venous ulcers. We report our clinical experience with 17 patients treated by CDP versus 9 patients treated by multilayered compression with short-stretch bandages in different time intervals.

PATIENTS AND METHODS

Patients

Seventeen venous leg ulcer patients with 17 target ulcers were treated with CDP while in the control group 9 patients received multilayered compression in an open, randomized, prospective, comparative, single center study. The study was approved by the Institutional Review Board of University of Szeged, Hungary.

Male and female patients above 18 years of age signed an informed consent form and agreed to participate in the study. Patients included were those with venous ulcers present for more than 3 months with at least a minimum width or length of 1 cm and ankle-brachial pressure index > 0.8. Patients having diabetic, arterial, or mixed ulcers, wounds showing local or systemic infections, decompensated heart or respiratory failure, active cancer, diabetic or ethanol-induced neuropathy, or insulin or non- insulin dependent diabetes were excluded. Use of antibiotics, immunosuppressants, cytotoxic agents, and venotonic drugs had to be avoided during the study period. No venous surgical interventions were allowed throughout the investigation.

Patients were evaluated on the basis of revised CEAP classification after clinical and color-Doppler ultrasound examination (41). Patient groups were matched in gender ratio, mean age, mean duration of chronic wound and mean ulcer sizes at baseline except mean age between groups 2 and 3. Key characteristics are seen on *Tables 1-2*.

TABLE 1
Comprehensive Characteristics of Groups 1, 2, and 3

Variable	Group 1	Group 2	Group 3	P1	P2
Male/female ratio	4/4	3/6	5/4	1	0.637
Mean age (ys)	64.87 (44-75)	70.77 (56-85)	56.33 (32-71)	0.14	0.015
Baseline Ulcer size (cm^2)	23.07 (0.75-65.94)	21.47 (5.88-43.96)	13.87 (1.93-51.84)	0.45	0.329
Ulcer duration (months)	25.37 (4-40)	15.88 (3-60)	6.11 (3-16)	0.101	0.145

P1= difference between groups 1 and 3 (control) and P2= difference between groups 2 and 3 (control).

TABLE 2
CEAP Classification of Groups 1, 2, and 3

Variable	Group 1	Group 2	Group 3	P1 value	P2 value
Clinical					
C6	8/8	9/9	9/9	-	-
Etiology					
Primary	6/8	8/9	8/9	0.57	1
Secondary	2/8	1/9	1/9	0.57	1
Anatomy					
Deep	2/8	2/9	3/9	1	1
Perforator	4/8	3/9	6/9	0.63	0.34
Superficial	5/8	6/9	7/9	0.61	1
Pathophysiology					
Reflux	7/8	8/9	9/9	0.47	1
Obstruction	2/8	2/9	1/9	0.57	1

P1=difference between groups 1 and 3 (control) and P2=difference between groups 2 and 3 (control).

Study Design

Assignment to treatment was performed in a randomized, prospective study. CDP was carried out in group 1 (8 patients) and 2 (9 patients). Each cycle consisted of 30 min MLD (29) after Vodder's method including the involved leg and periulcer region once daily in 5 or 10 subsequent treatment days in an inpatient setting. Wounds were then covered with sterile gauze dressing (Hartmann-Ricoh Hungary Ltd, Biatorbagy, Hungary). Subsequently, Rosidal Sys compression system (Lohmann-Rauscher, Germany) was applied to the affected limb.

Control group comprised 9 patients wearing Rosidal Sys compression.

Wound Care

Local treatment was standardized in the trial protocol and was the same for each patient regardless of which group they belonged to: cleansing of the ulcer base with Octenisept

(octenidine hydrochloride 1%, Schuelze and Meyr, Norderstedt, Germany) solution and application of wet to dry wound care. A wound care ointment comprising 1% salycilyc acid and 3% sodium tetraborate dissolved in white vaseline was applied. Wounds were covered with sterile, nonadherent gauze. Surrounding skin was treated with a protective zinc paste. Wound dressing was changed every day in both groups. After local treatment and occlusion of the ulcer, the compression system was applied in supine position.

Interface Pressure Adjustment

Bandages were used following the manufacturer's instructions and interface pressures measured at the point in the distal leg where the muscular part of the medial gastrocnemius meets the tendinous part. Measured values were 51 mmHg (range: 44 to 60 mmHg) and 50 mmHg (range, 42 to 60 mmHg) in groups 1 and 2, and 50 mmHg (range: 45 to 60 mmHg) in the control group at baseline. Kikuhime system (TT MediTrade, Denmark) was used for subbandage pressure measurement (24).

Study Outcomes

The primary objective of the study was the comparison of wound healing between the groups treated with CDP and the group using only adequate compression based on short stretch material. One major limitation of the study is the short term observation of ulcer healing.

The primary outcome was ulcer area reduction rate or, in other terms, healing rate (square centimeters per week). Wound area assessment was performed the measurement of the two perpendicular linear dimensions using a simple ruler. Using the wound length and width, we assumed an elliptical shape that moderately overestimates the real area. The following formula was applied to determine wound area: $\pi(a/2)(b/2)$, where a and b denote the major and minor diameters (42).

Statistical Analysis

Statistical analysis was performed with Fisher exact two-tailed test to characterize gender ratio and CEAP classification, two sample t-probe to compare mean age, baseline ulcer size, ulcer duration and area reduction rate. Analyses were made with Statistica 8.0 (Statsoft, Tulsa OK, USA) and P value <0.05 was considered as statistically significant.

RESULTS

At the end of observation periods, 3 ulcers in group 1 had completely healed. None of the chronic wounds showed symptoms of critical colonization or infection. The difference between the ulcer healing rate of group 1 (MLD+compression bandaging) and group 3 (compression bandaging alone) was not significant at day 5 (0.36 ± 0.23 cm^2/day and 1.14 ± 1.42 cm^2/day, respectively; df=15, p=0.12) (*Tables 3-5*). For illustration of the wound healing process over time see *Figs. 1 and 2*.

The healing rate of group 2 (MLD + compression bandaging) was more pronounced compared to group 3 (compression bandaging alone) at the end of the treatment (day 10) (0.29 ± 0.13 cm^2/day and 0.89 ± 0.73 cm^2/day, respectively; df=16, p=0.027).

DISCUSSION

The technique and tools of local wound care have rapidly evolved in the past decade. Despite the developing science of wound treatment, relatively "old fashioned" compression is the cornerstone therapy for venous-origin chronic wounds (43-45). The use of inelastic bandages provides a better prognosis for improvement of venous and lymphatic disorders (46). Furthermore, double-layered short stretch bandages did not prove to be inferior compared to multilayered bandaging systems (47). One of the major challenges in chronic wound care is the improvement of the relative efficacy of the various treatment steps

TABLE 3
Characteristics of Treatment Group 1 (DVT, MLD and C Denote Deep Venous Thrombosis, Manual Lymph Drainage and Compression Therapy, Respectively)

Patient	Age (yrs)	Gender	Previous DVT	Location of target ulcer	Treatment	Baseline area (cm^2)	Area at day 5 (cm^2)
1	59	M	None	Right leg	MLD+C	0.863	0
2	61	M	1x	Left leg	MLD+C	0.785	0
3	73	F	None	Right leg	MLD+C	2.82	1.69
4	62	F	None	Left leg	MLD+C	5.49	4.66
5	44	M	None	Right leg	MLD+C	31.4	21.76
6	75	F	None	Left leg	MLD+C	65.94	47.1
7	70	F	None	Right leg	MLD+C	76.53	63.74
8	75	M	None	Right leg	MLD+C	0.75	0

TABLE 4
Characteristics of Treatment Group 2 (DVT, MLD and C Denote Deep Venous Thrombosis, Manual Lymph Drainage and Compression Therapy, Respectively)

Patient	Age (ys)	Gender	Previous DVT	Location of target ulcer	Treatment	Baseline area (cm^2)	Area at day 10 (cm^2)
1	85	F	None	Right leg	MLD+C	7.45	3.14
2	82	F	None	Right leg	MLD+C	9.42	2.82
3	69	F	None	Right leg	MLD+C	5.88	4.71
4	60	M	None	Right leg	MLD+C	27.475	25.24
5	58	F	1x	Right leg	MLD+C	43.96	29.35
6	76	M	None	Right leg	MLD+C	47.1	21.98
7	76	M	None	Right leg	MLD+C	8.24	0.785
8	75	F	None	Left leg	MLD+C	13.73	4.71
9	56	F	None	Left leg	MLD+C	30	20.1

and cost-effectiveness of wound healing. The importance of the development of compression therapy must be underlined because it targets the reversal of the inciting cause, the chronic ambulatory venous hypertension. Chronic venous hypertension often leads to the exhaustion of lymphatic vessels and lymphedema (48). Compression therapy is the most useful tool to treat lymphedema that can be further enhanced with complex decongestive lymphatic therapy. There is abundant evidence to support that lymphatic insufficiency also plays a significant role in the maintenance of chronic wounds. Experiments studying lymph flow in various stages of chronic venous insufficiency have verified the active role of lymphatic insufficiency. Stewart and his co workers found increased contrast material uptake of inguinal

TABLE 5
Characteristics of Group 3 (Control) (DVT and C Denote Deep Venous Thrombosis and Compression Therapy, Respectively)

Patient	Age (yrs)	Gender	Treatment	Previous DVT	Location of target ulcer	Baseline area (cm^2)	Area at day 5 (cm^2)	Area at day 10 (cm^2)
1	50	F	C	None	Right leg	6.28	4.55	3.45
2	32	F	C	None	Left leg	9.29	7.25	5.91
3	53	M	C	None	Right leg	5.29	3.79	2.82
4	52	F	C	None	Left leg	1.93	1.29	0.27
5	69	M	C	None	Right leg	12.19	11.3	11.02
6	65	M	C	1x	Left leg	7.03	6.14	4.28
7	55	M	C	None	Left leg	4.71	3.61	2.82
8	71	F	C	None	Left leg	51.84	48.08	46.72
9	60	M	C	None	Left leg	26.29	22.6	21.41

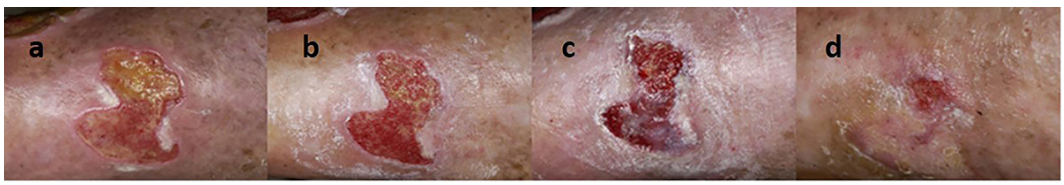

Fig. 1 Venous leg ulcer healing in a 77 year-old female patient using a 5-day course of manual lymph drainage adjunctive to compression bandaging of the right leg (a. day 0, b. day 5, c. day 28, d. day 40)

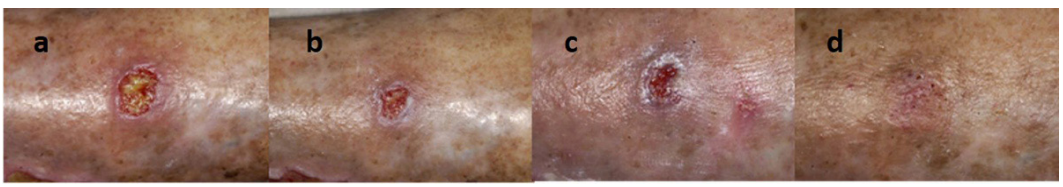

Fig. 2 Venous leg ulcer healing in a 75 year-old female patient using 10-day course of manual lymph drainage adjunctive to compression bandaging (a. day 0, b. day 10, c. day 28, d. day 40)

lymph nodes in chronic venous insufficiency (49). Partsch and his group demonstrated the severe insufficiency of lymph flow in the area of leg ulcers and severe lymphatic insufficiency in dermatoliposclerotic regions. The more advanced stages of venous insufficiency caused the more pronounced tracer uptake of regional lymph nodes suggesting the compensatory mechanism of deep lymphatic collectors (50). Mortimer and his colleagues found impaired lymph flow in the persistent venous leg ulcers (51). This particular study did not distinguish among the clinical stages of lymphatic insufficiency and, therefore, did not measure lymph flow within the subgroups. Vital microscopic study displayed irregular lymphatics and the leakage of contrast media into the pericapillary space. Morphology studies were in accordance with the observations of functional experiments. Superficially, lymphatics are almost completely absent within the ulcer base. Much deeper, lymphatics are present sporadically whereas at the ulcer margin in a much higher density. Periulcer lymphatics show morphological (20) and functional damage (21). Due to the abundant volume of interstitial fluid and handicapped lymphatics, the lymphatic transport capacity is decreased. In lipodermatosclerotic skin, the morphologic changes suggest that the markedly disturbed absorption of interstitial fluid likely contributes to slow healing and high recurrence rate of chronic venous stasis associated ulcers. The poor lymphatic network within leg ulcers exhibit impaired regenerating capacity after healing and scar formation. In secondary intention healing, the formation of scar tissue greatly prevents the ingrowth of lymphatic vessels into the ulcer from undamaged surrounding tissue (52). Even though it has also been observed that lymph vessel neovascularization occurs within scar tissue, their capacity and diameter lags behind normal lymph vessels (3,7,9,10,52-55). In the description of leg ulcers, the periulcer region is often not thoroughly examined. Surrounding edema is usually due to lymphatic insufficiency. Regarding venous leg ulcers, in more than 80% of the cases, generalized leg or periulcer local lymphedema can be found (3), and pericapillary microedema in granulation tissue can be observed in various origin ulcers (4). Edema increases the distance between capillaries and cells, and this distance between tissue channels affects metabolic exchange, causing a shift toward anaerobic metabolism. The exchange of gases and nutrients between plasma membranes is likely to be affected. The delivery of inhibitory factors of wound healing (e.g., toxins, white blood cell wastes) in lymphatic vessels is hampered (3). Removal of excess fluid from chronic wounds also removes inhibitory factors present in the fluids. Several studies have demonstrated that excess interstitial fluid suppresses the proliferation of keratinocytes, endothelial cells, and fibroblasts (56-58). As a result of edema reduction, the density of capillaries increases (56,57) but this angiogenesis is largely ineffectual (57). Regarding effective capillary proliferation, this alteration of microcirculation increased capillary filtrate that translates to elevated transportable fluid via lymph vessels. Both MLD and IPC reduce the capillary filtration rate (59-61). The sympatholytic effect of MLD causes dilatation of small arteries and enhances tissue perfusion but also increases the amount of interstitial fluid. Compression bandaging can restore the balance (62-64). Tissue perfusion can be increased by adequately applied compression bandaging (59,64) which is due to improved microcirculation. Various methods of compression including IPC drastically improve lymph flow (28,60,65,66).

Our primary goal was to further promote compression therapy so as to achieve more rapid ulcer healing. The basic theory of adjunctive MLD is to improve the damaged safety valve function of lymphatics in the chronic wound area. These treatments showed that the edema at the ulcer base and margin can be efficiently removed and tissue fluid imbalance partially reversed. MLD acts not only on decongestion and tissue fluid balance maintenance, it also increases tissue oxygenization via the improved of microcirculation,

softens fibrosis, causes vasodilatation of small arterioles, and has no damaging effects on peripheral lymphatics (67). An essential point that should not be forgotten is that lymphangiogenesis is an important process in wound healing. Recent data show that the flow of interstitial fluid is an essential guide for lymphangiogenesis (68). Decreased interstitial flow in secondary lymphedema coincides with poor lymphatic regeneration. Reduced interstitial flow suppresses endogenous lymphangiogenesis. Lymphatic endothelial cell migration follows the direction of lymph flow from distal to proximal. MLD is known to be the most efficient tool to direct lymph flow. Theoretically, it further enhances lymphangiogenesis leading to faster ulcer healing and reduction in recurrence rate of chronic wounds.

MLD as an adjunctive therapy to compression appeared to considerably accelerate recovery of venous origin chronic wounds in a longer (10-day) treatment period. A possible criticism is that the primary end point of our study was not complete healing of chronic wound and that the observation period was restricted to the course of decongestive therapy. MLD-based CDP appears to have a direct influence on ulcer healing during the treatment period. Long-term effects have not yet been determined. One can speculate that the MLD-induced process may have sustained effects that can be maintained by properly applied compression. Basically, we believe that MLD-caused effects exist as long as decongestive physiotherapy lasts. Ulcer healing was assessed on the basis of healing rate. A second possible criticism is that the measurement of wound area that was determined with a ruler converting data to an ellipse. This is a minor limitation, and calculated wound area compares favorably to area measured by computerized planimetry (69,70). A third and final justified criticism is that our study size is small, and further investigation will be needed in a larger cohort to confirm our preliminary findings and conclusions.

CONCLUSION

To our knowledge, this the first comparative study that verifies the adjunctive role of MLD in the conservative approach to chronic venous insufficiency based leg ulcers. This finding suggests the routine consideration of decongestive physiotherapy in the treatment of venous origin chronic wounds.

ACKNOWLEDGMENT

This work was supported by the Hungarian OTKA Fund 5k551.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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