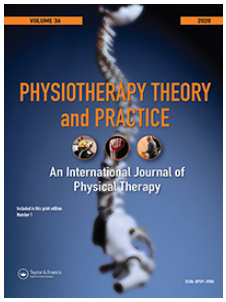

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RESEARCH REPORT

Low-frequency vibrotherapy considerably improves the effectiveness of manual lymphatic drainage (MLD) in patients with lipedema: A two-armed, randomized, controlled pragmatic trial

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ABSTRACT

Purpose: Although the exact prevalence of lipedema is unknown the number of women suffering from this condition is ever-growing. When treated conservatively, manual lymphatic drainage is regarded the gold standard. However, the rate of its effectiveness varies considerably with some women showing minimal to no improvement depending on severity of the disease and medical history. **Methods**: Thirty female patients diagnosed with lipedema stage 2–3 referred to physiotherapeutic treatment were randomly allocated to either six treatments of MLD or to six treatments of combined MLD and vibrotherapy treatment. Outcome parameters were the volume of lipedema at four locations of either the lower (n = 29) or the upper extremities (n = 1), as well as quality of life. **Findings**: A very large superiority of effectiveness was found for the combined treatment. Reduction of the sizes of lipedema varied between $1.1 < d < 3.2$. These patients' quality of life was also considerably better (d = 1.0). **Conclusions**: Combining MLD with vibrotherapy treatment drastically enhances the effectiveness of treating lipedema.

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Lipedema; MLD; quality of life; shock wave vibrotherapy

Introduction

Lipedema is a chronic and progressive disease characterized by a disproportionate, symmetrical swelling of subcutaneous adipose tissue in the lower and, to a lesser degree, in the upper extremities of predominantly women. The disease is often painful and, if left untreated, may cause multiple secondary health problems (e.g. mobility impairment). Both etiology and prevalence are largely unknown. However, lipedema usually develops early in puberty and is moderately correlated with hereditary hormonal disorders (Child et al, 2010). At later stages, some of the typical clinical features are: (1) small fatty nodules within the tissue; (2) bulges of fatty tissue above the knee; (3) swelling of the limbs throughout the day; and (4) sensitivity to pressure and easy bruising.

Lipedema has received relatively little scientific attention in the past. This is in part due to the fact that it is commonly misdiagnosed as (bilateral) lymphedema, extreme cellulitis, or morbid obesity (Földi and Földi, 2010; Sze, Kemeny, Groma, and Szolnoky, 2014). Lipedema develops as a result of fatty tissue that triggers excessive compression of the superficial lymphatic collectors. In women suffering from lipedema, the inhibition of the lymphatic system's primary function (i.e. the removal of interstitial fluid) may trigger the build-up of edema resulting in lipedema (Bae, Young-Joo, Jeong, and Kim, 2011). This condition aggravates over time because the ongoing strain on the lymphatic system causes further functional and possibly structural deterioration. At advanced stages, lipedema progresses through the same stages as lymphedema and is therefore diagnosed accordingly (Morgan, 2008). It is important to note that lipedema is a fairly common disease that is often misconceived and thus misdiagnosed (Buck and Herbst, 2016).

The exact prevalence of lipedema is unknown, but some epidemiologic studies report the following rates: 8% (Schubert and Viethen, 2016), 11% (Bae, Young-Joo, Jeong, and Kim, 2011), 15% (Herpertz, 1997), and 19% (Forner-Cordero, Szolnoky, Forner-Cordero, and Kemény, 2012) depending on the type of population investigated. In the recent past, research in this disease has been slowly growing, mainly because more and more women seek help. However, lipedema has as yet not been included in the International Classification of Diseases (ICD) by the World Health Organization.

Active treatment of lipedema is recommended at early stages in order to improve the patient's long-term prognosis. Invasive treatment (e.g. liposuction) usually only becomes necessary at late stages when the

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physical and physiological impairments are too burdening or when the patient does not respond to conservative treatment. Non-invasive/conservative treatment, on the other hand, aim at reducing edema, alleviating pain and hypersensitivity, and at increasing mobility when the patient still has a chance to reduce or maintain the size of the affected body parts. When treated conservatively, complete decongestive therapy (CDT) is regarded the gold standard for treating both lymphedema and lipedema (Forner-Cordero, Szolnoky, Forner-Cordero, and Kemény, 2012; Mayrovitz, 2009). There is a general consensus among experts that CDT is safe and effective (Hinrichs et al, 2004; Koul, Dufan, Russel, and Cooke, 2007; Lasinski, 2002). Its main effects consist of: (1) reduction of swelling; (2) increase of lymph drainage from the congested areas; (3) reduction of skin condition; (4) improvement of the functional status; and (5) improvement of quality of life (National Lymphedema Network, 2011).

One integral part of CDT is manual lymph drainage (MLD). There are several "schools" of MLD (e.g. Vodder, Földi, or Leduc), but they all share common features and do not significantly differ. At its core, MLD aims at stimulating superficial lymphatic vessels to remove excessive interstitial fluid. To do so, the therapist applies gentle, pumping, circular movements using low pressure. In addition to MLD's effects on the lymphatic system (e.g. transport capacity, fluid flow, and reduction of interstitial pressure/volume), it has positive effects on other physiological systems like the arterial system, the autonomic nervous system, or the urinary organs. Overall, the results from MLD are rather long-term requiring the patient to adhere to continuous treatment. However, the effects may vary depending on the type of location, comorbidity, and cause of the damage of the lymphatic system (Huang et al, 2013; Lasinski et al, 2012). In patients with lipedema, the lymphatic system appears to respond equally to MLD, but the reduction of subcutaneous fatty tissue responds, if at all, rather slowly. This is why different forms of compression may be required (i.e. the second component of CDT), which may help to reduce excessive fat tissue (Child et al, 2010).

The lymphatic system can be stimulated via different routes. Specifically, there are devices that produce vibrational impulses and waves, which aim at altering cell functioning. In the physiotherapeutic practice, such devices have mainly been applied to treat pain, but the body of evidence is rather inconclusive (Seco, Kovacs, and Urrutia, 2011). However, such devices typically use high and low energetic radial impulses and typically only apply local and punctual energy. The present study was conducted to test the effects of the transmission of mild, vertical, low–frequency impulses (Cellconnect Impulse).

Method

Study design and procedure

The study was a two-armed, measurement repeated, randomized, and controlled pragmatic trial. The balanced random allocation sequence was generated using the software package SPSS 17. The random allocation sequence was implemented by a patient sequence list accessed by the therapists before each session. Treatment was performed by a female and a male physiotherapist. Both treated 15 patients each, and were randomly assigned to them. The therapists had a professional experience with lipedema of more than 25 years.

To test the effectiveness of the interventions under routine practice conditions, patients were treated in accordance with German medical health care and prescription regulations, receiving six treatments of 30 minutes each. In the initial session, the physiotherapist introduced the nature and purpose of the study. After patients gave their informed consent, baseline measures were taken. Then, participants were informed about the type of treatment they received according to the randomization protocol. Subsequently, the first treatment was applied. The therapeutic intervention comprised two treatments per week, totaling three weeks per patient. Upon the last treatment, post-treatment measures were taken to determine the therapeutic outcome.

Sample

Patients were recruited from the patient base of a local physiotherapy practice. Participation required a condition that had been diagnosed by a medical expert (i.e. a phlebologist) and at least stage 2 in accordance with the recommendations of to the Fifth WHO Expert Committee (Morgan, 2008). A total of 31 women were enrolled in the study (Figure 1). One woman discontinued her involvement after the first treatment due to personal reasons not further specified. Twenty-seven women were diagnosed with stage 2, three were diagnosed with stage 3. None of the patients suffered from a major acute health threatening disease (e.g. cancer, acute infection or major injury), drug addiction, or mental illness, all of which were considered exclusion criteria. From the 30 patients, 16 applied compression bandaging on a daily basis, varying between three to 24 hours. Seventeen women were under regular medical treatment, which had endured for 3–26 years.

The mean age of the sample was 53.2 years (range: 23–75 years). Mean weight was 91.2 kg (SA: 20.4),

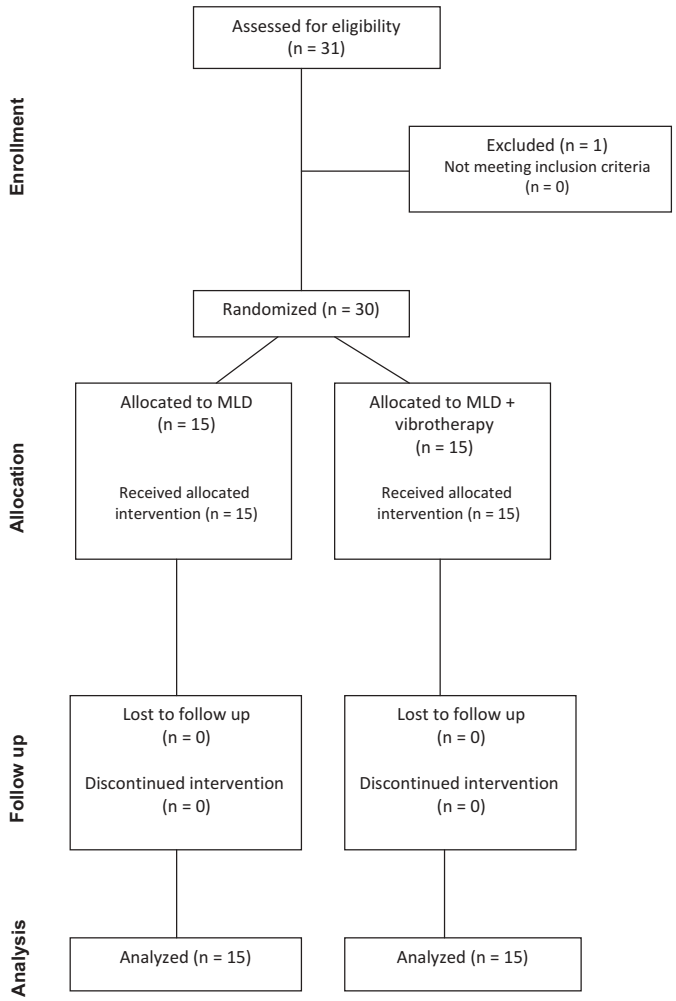

Figure 1. Flow diagram of randomized and analyzed patients.

mean height was 164.9 cm (SA: 6.6), and the mean BMI was 35.6. On average, patients suffered from lipedema for 12.5 years (SA: 9.1 years). From the 30 women, 22 reported symptom-associated pain in their limbs, 19 showed signs of impaired limb flexibility. In 12 patients, the skin showed signs of alterations (e.g. discoloration and hyperplasia). The study was run according to the Ethical Principles for Medical Research Involving Human Subjects and the CONSORT for Pragmatic Trials (Zwarenstein, 2014). All participants provided written informed consent.

Assessment

Size of lipedema

According to recommendations for volume measurement (Chen, Tsai, and Jung, 2008; Ng and Munnoch, 2010), patients suffering from lipedema in the lower extremities (n = 29), were tape measured bilaterally in a lying position at four sites: (1) forefeet, (2) ankles, (3) calves (six inches above the ankle), and (4) thighs (six inches above the knee). In one patient showing signs of lipedema in the upper extremities, circumference was tape measured on the following sites (bilaterally): (1) palms, (2) wrists, (3) forearms (six inches above the wrist), and (4) upper arms (six inches above the crook of the arm). Bilateral measurements were averaged to obtain the mean circumference for each location.

Health-related quality of life

The questionnaire "Quality of Life with Chronic Disease" (German: "Profil der Lebensqualität chronisch Kranker" [PLC]) (Siegrist, Broer, and Junge, 1996) measures the quality of life experienced by patients

with chronic diseases on the physical, emotional and social levels, making allowance for subjective state of health and action abilities. The PLC offers valid and reliable indicators of the degree of restriction or disability experienced by patients. Its administration renders practical results in the clinical and therapeutic realm, especially when symptoms are assessed over the course of time. The main module differentiates between six basic dimensions from which the first four were considered in the present study: (1) physical performance; (2) ability to relax (positive and negative mood); (3) ability to communicate; and (4) sense of belonging. Each item consists of a 5-point-Likert-scale with the anchors very bad, bad, moderate, good, and very good.

Moderating variable

Before the treatment, patients were asked to assess the degree to which they thought their symptoms would improve with the treatment. Specifically, they were presented with five self-constructed rating scales assessing: (1) bodily impairments; (2) physical quality of life; (3) well-being; and (4) symptom-related stress. Additionally, they were asked to rate the expected effectiveness of the intervention. Each item consisted of a 4-point-Likert-scale with the anchors not at all, hardly, somewhat, and very much. All five items were summed to determine a global index. At the end of the trial, patients were presented with the same items and asked to rate the actual state they were in (e.g. the extent to which the expectations came true).

Treatment/intervention

Manual lymphatic drainage (MLD)

This treatment involved slow, gentle, rotary, "pump" and "scoop" hand movements stretching the skin of the affected areas in centripetal directions and allowing it to return to its normal position. The MLD sequence started proximally and centrally. Functional and unaffected (non-edematous) inguinal lymph nodes were treated proximally to stimulate overall lymph function. Due to the strong pain associated with it, deep abdominal lymphatic vessels and nodes were not involved in the MLD treatment. Patients were treated for 30 minutes per session.

Vibrotherapy

Patients undergoing this treatment received the same MLD described above. During MLD, however, they were placed on an adjustable, full body table (204 × 88 cm^2) that mechanically transmitted smooth, vertical, low-frequent, shock impulse waves produced by the motor underneath the table according to a standardized software program (Cellconnect Impulse; Patent Nos.: EP 16 000 704.3, EP 12 783 861.3, DE 10 2015 003 854.0, DE 10 2011 117 680.6). The impulses involved no administration of electric or electromagnetic energy, but instead only comprised physical vibration, which disperse as smooth micro fluctuations through bodily fluids and cells thereby altering cell function and metabolism (e.g. nutrient transport, detoxification, and regeneration). Before starting the session, patients were asked to use the bathroom. Then they were asked to drink 300 ml of table water to facilitate metabolic excretion. The program started with a low frequency of 15 Hz, which was automatically increased in intervals of three minutes up to a maximum of 42 Hz.

Data analysis

In alignment with meta-analytical practice (Hunter and Schmidt, 2004), and to avoid pseudo evidence associated with the use of NHST, effect sizes and confidence intervals were calculated. Specifically, mean comparisons were analyzed according to Cohen's d effect size (Cohen, 2008). Confidence intervals (95%) were calculated to estimate the boundaries of the effects (Borenstein, Hedges, Higgins, and Rothstein, 2009). To assess differential effects between the interventions, difference scores (post treatment minus baseline) were compared.

Results

Expectation

Before the treatment, patients in the MLD group descriptively showed a stronger expectation regarding the therapeutic outcome than those in the combined treatment group. On a scale of 5–20, their mean expectation was 13.6 (SA 3.9), while that of the Add-on group was 12.2 (SA 3.3). The difference between the groups was small to medium (d = 0.4), but fell within negative 95% CI boundaries. After the treatment, the mean score in the MLD group had dropped to 12.3 (SA 2.9), while the mean of the combined treatment group elevated to 16.8 (SA 2.1). This difference was very large (d = 1.8; 95% CI: 1.2 < d < 2.3) and indicated that patients undergoing the combined treatment were much more satisfied with the therapeutic outcome.

Size of lipedema

Table 1 and Figure 2 show the differences between both treatment groups. As can be seen, the reductions of the

Table 1. Means and standard deviations of circumference of lipedema at baseline and after six treatments.

	MLD†				Add-on			
	Baseline		Post-treatment		Baseline		Post-treatment	
Forefeet *	23.8	1.6	23.6	1.5	22.9	1.3	22.3	1.4
Ankles	26.6	2.3	26.4	2.1	25.5	2.5	24.3	1.9
Calves	42.1	4.1	41.5	4.2	42.8	3.6	41.0	3.2
Thighs	58.2	8.0	57.7	7.9	61.8	9.8	59.2	9.6

† MLD: manual lymphatic drainage; Add-On: vibrotherapy + MLD. *Rounded values; $n = 29$.

size of lipedema from baseline to post-treatment were much smaller in the MLD group. The changes in the MLD group varied between 0.2 and 0.6 cm, those in the combined treatment group varied between 0.6 and 2.6 cm. The analyses of the differential effects yielded large to very large effects. For the reduction of the circumference of the forefoot, the effect was $d = 1.1$ (95% CI: $0.5 < d < 1.6$). The effect of the reduction of the ankles was $d = 1.2$ (95% CI: $0.6 < d < 1.7$), that of the calves was $d = 1.7$ (95% CI: $1.1 < d < 2.3$). The largest effect was found for the reduction of lipedema of the thighs (d = 95% CI: 2.3; $1.6 < d < 2.9$). The size of the latter effect amounted to a 99% superiority of the combined treatment vis-à-vis the MLD treatment (i.e. 99% of the patients showed an improvement that was larger than the average of the patients receiving MLD alone). The analyses comprising the total sample of patients involving the woman suffering from lipedema in the upper extremities basically yielded the same results (forefeet/palms: $d = 1.1$; ankles/wrists: $d = 1.2$; calves/forearms: $d = 1.4$; thighs/upper arm: $d = 2.3$).

Quality of life

Table 2 and Figure 3 depict the mean ratings for the quality of life dimensions before the first and after the last treatment. Consistent with the results from the reductions of the size of lipedema patients receiving the combined intervention reported a higher quality of life at the end of the treatment. The effects for physical performance were $d = 0.7$ (95% CI: $0.1 < d < 1.2$), for negative mood it was $d = 0.8$ (95% CI: $0.1 < d < 1.6$), and for the ability to relax it was $d = 1.1$ (95% CI: $0.4 < d < 1.9$). For positive mood it was smallest and fell within negative 95% CI boundaries ($d = 0.5$, $-0.01 < d < 0.9$). To assess the overall quality of life, all four scales were combined and subjected to the analyses. There was a large effect of $d = 1.1$ (95% CI: $0.5 < d < 1.6$), indicating that patients undergoing the combined treatment benefitted more than those receiving MLD alone. Quality of life only improved about 8% in the MLD group and about 23% in the group receiving the Add-on treatment.

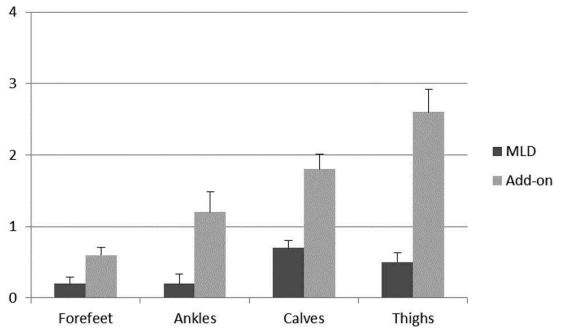

Figure 2. Mean circumference reductions and standard errors for manual lymphatic drainage and the Add-on therapy (MLD and vibrotherapy).

Discussion

The aim of this pragmatic trial was to determine the effectiveness of a new form of vibrotherapy within a routine outpatient practice treating lipedema. Overall, the classical form of treatment (MLD) yielded negligible improvement rates. The average effect size for the reduction of lipedema was $d = 0.1$. In other words, there was no symptom improvement. However, these results are not too surprising given that the women in this sample had a rather long medical history and showed various signs of aggravated symptom progression. One could argue that rather than improving symptoms associated with lipedema maintaining the status quo and/or preventing deterioration should be regarded the primary therapeutic outcome. From this point of view, the results observed are in alignment with general clinical experience and empirical evidence regarding the effectiveness of MLD in women with a long medical record of lipedema. In fact, for most patients in this trial, frequent visits to health care professionals and continuous treatment were mandatory and an integral part of their life to maintain their status quo.

Against this backdrop, the changes observed in patients receiving the combined treatment were very surprising. The effects found were large to very large in comparison to MLD alone, and remarkable both from a statistical and a clinical point of view. Moreover,

Table 2. Mean and standard deviations of quality of life at baseline and after six treatments.

	MLD				Add-on			
	Baseline		Post-treatment		Baseline		Post-treatment	
Physical performance*	15.0	6.6	17.5	5.9	16.9	4.4	21.9	3.5
Ability to relax*	17.3	5.0	18.3	5.8	19.7	3.3	23.5	3.0
Positive mood **	8.7	4.0	9.9	3.8	10.6	3.0	13.5	2.3
Negative mood *	19.6	6.3	19.9	7.3	21.6	4.0	25.6 †	4.5

* Scale range: 0–32. **Scale range: 0–20. †Inverse coding (i.e. higher values indicate improvement).

patients were only treated for six sessions which is a rather short period of treatment regimen. Obviously, simultaneously receiving physical stimulation of the whole body through low-frequency impulses either potentiated the effects of MLD or caused specific effects over and above MLD. Interestingly, these results are consistent with the effects observed in a recently conducted pragmatic trial with patients suffering from chronic back pain (Schneider, 2018). It appears that smooth, shock impulse waves exert a positive effect on the lymphatic system. This became evident in the clinical observation that in all women a strong urge to urinate was produced after each of the six treatments. Also, this urge persisted during the following 24 hours indicating a heightened fluid excretion.

Treating lipedema with shock waves is a relatively new concept, which has not yet been incorporated in the general physiotherapeutic treatment regimen. In fact, Cellconnect Impulse is the first form of vibrotherapy applying a special form of impulses. Most shock wave devices typically apply high and low energetic radial impulses and only apply local and punctual energy. Cellconnect Impulse is different in that it uses smooth impulses of varying frequency rates that affect the whole body.

Clearly, the nature of the study does not allow discussing the exact mechanisms of the effectiveness of the device. It is conceivable that, based on the physiology of the lymphatic system and the effects generated by vibration, the alterations stemmed from lowering the interstitial pressure, opening the lymphatic capillaries, and/or traction of myofilaments. However, at this point this is mere speculation.

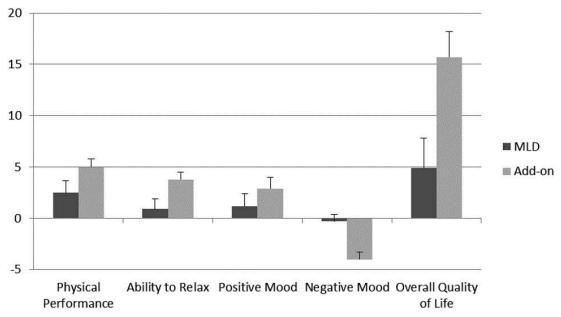

Figure 3. Mean health related quality of life dimensions and standard errors for quality of life dimensions (scale values) after manual lymphatic drainage (MLD) and the combined treatment (vibrotherapy + MLD).

The study was conducted to compare the outcome of two forms of interventions similar to a Phase-III study of a clinical trial. Nonetheless, the results show that a widely accepted standard treatment (i.e. MLD), which is regarded the gold standard can be considerably enhanced even in patients with a long medical history and in a very short number of treatments.

Several open questions could not be addressed in this study. First, since it was designed as a pragmatic trial, the efficacy of Cellconnect Impulse could not be determined. The size of the effects in a more controlled environment is therefore unclear. However, from a practical point of view, this might be less relevant. In this trial, treatment was standardized regarding type of MLD, treatment duration and software program. Thus, the fact that such clear differential effects were found underscores the superiority of this type of treatment.

Second, the exact nature of the effect is unknown. As mentioned above, the effect of this vibrotherapy might be auxiliary, potentiating or specific. These mechanisms should be dissected in studies involving several treatment arms involving a zero control group (or waiting group) and one group treated exclusively with this new vibrotherapy. The latter arm would also help to disentangle specific and non-specific (psychological) effects (Schneider and Kuhl, 2012). It should be noted, though, that blinding or masking of the treatment is neither pertinent nor feasible to investigate such non-specific effects. Although expectation does not appear to have a significant effect in this type of treatment, there might still be other confounds contributing to the overall effect (e.g. the therapist and regression effects). Third, to explore the underlying mechanisms in more detail, additional diagnostics should be employed (e.g. imaging techniques for the soft tissue – MRI, CT, or ultrasound; lymph vessel imaging – lymphoscintigraphy; or electrical conductance testing – bioimpedance spectroscopy). Such diagnostics could also help complement the herein reported mode of measurement. Although circumference measurements are common and standard in most

physiotherapeutic practices, they may be prone to measurement errors. However, such measurement errors only become problematic if they are unsystematic; in other words when the therapist intentionally alters the measurement sites. Fourth, it is unclear how long the effects of vibrotherapy treatment last. Although, the treatment effect already showed after six sessions, it would have to be determined if and how long it persists, and if it is able to reverse the clinical symptoms. Although the medical condition of lipedema is regarded progressive and conservative treatment at best prolongs symptom aggravation, there is anecdotal evidence supporting the notion disease remission is possible when treated with vibrotherapy. However, stringent and well-controlled investigations are needed to corroborate this issue.

Limitations

This study was funded by the company manufacturing this form of vibrotherapy (Cellconnect Impulse) and therefore, in principal, the investigators representing the research and consulting firm could have been biased with regard to the outcome. To make sure that this was not the case the principal investigator was not involved with the actual treatments and had no contact with the patients. Also, all collected data were initially blinded as to the group allocation and only unblinded after the analyses were performed. Lastly, the study was run under the recorded stipulation that it be published independent of the outcome.

Conclusion

The present study is the first to show that combining MLD with a new vibrotherapy treatment provides a therapeutic advantage in treating lipedema. The effects are large, fast-acting compared to conventional therapies, and impact volume of the affected sites and health related quality of life.

Conflict of interest

The authors was not directly employed by Cellconnect Inc., but represented an independent research and consulting firm.

Funding

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