

Application of microcurrents of bioresonance and transdermal delivery of active principles in lymphedema and lipedema of the lower limbs: a pilot study

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Aim. Application of microcurrents of bioresonance may allow protein aggregates lysis and a related enhancement of lymphatic drainage. Combining bioresonance with transcutaneous passage of active principles, by means of skin electroporation, microcirculation and clearance of connective tissues may be theoretically activated. A pilot study on an electro-medical device which includes these two technologies (Transponder®), has been performed on patients affected by lymphedema (LYM) and/or lipedema (LIP) of the lower limbs.

Methods. Eight patients affected by primary or secondary unilateral LYM or LIP were submitted to six consecutive daily sessions with the medical device; the first two sessions were performed by a trained physiotherapist, whilst the following four sessions were self-administered by the patients themselves at home (who were educated about the technique). Magnesium silicate was delivered transcutaneously by means of the device at each session. Pre-post-treatment assessment included: 1) limb volumetry by means of tape measurement; 2) segmental multifrequency bioimpedance spectroscopy for fluid changes, with L-DEX measurement; 3) visual analogue scale (VAS) (0-10 score) questionnaire for related symptoms.

Results. All the patients completed the scheduled treatment. After the treatment the mean volume of the whole limb decreased from 9462,85 (SD±3407,02) to 9297,37 cc (SD±3393,20), which accounts for a 165,48 cc (2%) reduction after six days of treatment. The pre/post-treatment VAS mean score changes were: heaviness from 4.57±3.46 to 2.43±2.57 (-47%), dysesthesias from 1.71±2.63 to 0.71±1.50 (-58%), pain from 1.57±2.57 to 0.57±0.79 (-64%). Diuresis VAS measurement passed from 7.43±1.81 to 8.57±0.98 (15% increase). The average L-DEX percentage reduction was 21%. No side effects were reported and a good patients' compliance was recorded.

Conclusions The preliminary data of this pilot study show

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that the combination of microcurrents of bioresonance with transdermal delivery of active principles indicate that it could result in edema decrease and symptom improvement in patients affected by LYM and/or LIP of the lower limbs. Self-administered modality of the electrical device is possible and effective; no side effects have been reported.

KEY WORDS: Lymphedema - Lower extremity - Administration, cutaneous.

Lymphedema (LYM) of the extremities may be of primary (genetic origin), or secondary nature (after surgery, such as lymphadenectomy in neoplastic surgery, after infections, traumas etc.) Primary LYM may be due to hypogenesis or hypoplasia of the main lymphatic vessels/nodes and it is largely underestimated worldwide; LYM may be associated to venous edema (phlebolymphedema) mostly in post-thrombotic syndrome, in late stages of varicose veins, or after traumas.¹

From the pathophysiology point of view LYM is a high protein volume edema, as lymphatic system is delegated to the reabsorption of larger molecules (proteins, bacterias, etc.). Recent researches highlight an extremely important role played by the lymphatic system in the fluid homeostasis within the vast majority of the tissues of the human body.²

LYM is basically the result of a mechanical and/or functional deficit in the physiologic lymphatic drainage. Diagnosis of LYM is usually of clinical kind,

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but colour-duplex ultrasound (CDU), multifrequency bioimpedance analysis and especially lymphoscintigraphy play a major role to define the anatomical and lymphodynamic pathologic changes in the edematous regions.

From the therapy point of view, LYM is usually approached through an holistic treatment, of a multifaceted nature (complex decongestive therapy, CDT), which is based on manual lymphatic drainage, compression by means of bandages/garments, pharmacologic treatment through benzopyrones^{3, 4} and electromedical devices, such as intermittent pneumatic compression. Skin care and specific exercises usually complement the complex treatment.^{5, 6} Most treatments are aimed to remove/reduce the stagnating protein aggregates, to enhance lymph flow in the residual lymph routes, and to combat fibrosis as well. Among electromedical devices, new machines have been proposed more recently.⁷⁻⁹ Finally exeretic or reconstructive surgery usually have a limited space and mostly in non-CDT responder cases of LYM.⁵

Lipedema (LIP) is a form of edema of the lower (more rarely upper) limbs, which is linked to an abnormal fat deposition, to lipodystrophic changes in the subcutaneous tissues mainly; these changes eventually result in fluid retention, especially in the lower legs. In later stages an impairment of lymphatic drainage has been highlighted, both for functional overload and for organic changes in the lymphatic capillary net¹⁰. LIP has a strong inherited component and is more prevalent in women, though epidemiology data are lacking. Treatment of LIP seems to provide transient benefits to patients in many cases and recurrence rate is quite high, especially in non compliant patients. Therapy of LIP is mostly based on the same treatments which have been detailed above for LYM, though surgery, under the form of liposuction, seems to provide some improvements.^{11, 12}

With reference to the electromedical devices, literature data show that microcurrents may induce an activation of bioresonance activities of the tissues, with a resulting breaking of the interstitial protein aggregates, the re-routing of the catabolites towards the lymphatic capillaries and a loco-regional activation of the lymphatic system.¹³

Also a possible positive effect of a few active principles through the skin has been demonstrated in past studies.³ Similarly the possibility to increase the passage of active substances through the skin through electroporation has been shown more recently.¹⁴

On the basis of these chemical-physical advancements, a specific medical device (Trasponder®) has been designed with the aim to improve veno-lymphatic microcirculation and tissue clearance (see picture n.1). More in details bioresonance activity induced by specific microcurrents (Biphasic Square Wave; port. 0.3 Hz÷6.2 Hz; modulant. 400 Hz÷2100 Hz; 14 mA on 500 ohm) has been coupled with application of magnesium silicate on the skin of the affected area, with the aim to enhance the transdermal passage of these and other substances which may be potentially of help in LYM and/or LIP.

The aim of this pilot study was to assess efficacy and safety of this new technology on patients affected by lymphedema and/or lipedema of the lower limbs, who received and self-administered the treatment by means of a specifically designed portable electro-medical equipment

Materials and methods

A pilot observational study was performed to assess results and possible side effects of a newly developed electro-medical device (Trasponder® Figure 1), which is based on the application of microcurrents of bioresonance and transdermal delivery of



Figure 1.—Trasponder® electro-medical device.

TABLE I.—*Inclusion and exclusion criteria.*

Inclusion criteria
– Primary or secondary unilateral lymphedema (stage I-II-III) of the lower limb and/or lipedema of the lower limbs
Exclusion criteria
– Any complex decongestive treatment performed in the last 2 months
– Active neoplasms under treatment
– Renal, cardiac or liver failure
– Current treatment with calcium antagonists and/or alpha-lytics or corticoids
– Acute deep or superficial vein thrombosis, or acute dermatolymphangioadenitis (erysipelas, lymphangitis)

active substances, plus vacuum-suction mechanism, on patients affected by LYM and/or LIP.

Eight patients (5 women, 3 men; mean age 51.86 ± 18.78 years) have been enrolled in a preliminary study, whose inclusion criteria and exclusion criteria are listed in Table I.

All patients were required to wear compression garments (20-30 or 30-40 mmHg at the ankle site, according to the degree of edema) in the last two months before the inclusion and during the clinical study.

More in detail 6 patients (3 males and 3 females, mean age 56.60 ± 20.32 , mean BMI 34.00 ± 6.04) had unilateral LYM of the lower limb and 2 patients had bilateral LIP of the lower limbs (2 females, mean age 40.00 ± 8.49 , mean BMI 22.00 ± 4.24). Each patient underwent one treatment session of 45' per day for six consecutive days; the first two treatments were performed by a physiotherapist who also instructed the patient on the technique to adopt when using the device at home. In the following four days the treatment was performed by the patient himself/herself by using the portable machine at home. All patients signed an informed consent and were informed about the technical characteristics of the battery-operated electromedical device and on the manual application needed to treat the edematous limb.

Pre-post-treatment investigation included:

1) tape measurement of the lower limb (six measurements, with 12 cm interval, starting from the medial malleolus salience) and relative segmental limb volume calculation on the basis of the following truncated cone formula:⁴

$$\frac{h (C_1 \times C_1 + C_1 \times C_2 + C_2 \times C_2, \text{etc.})}{12\pi (\pi = 3,14)}$$

where h is the distance between the two consecutive circumferences (12 cm in our study), C1 is the

most distal circumference (e.g. immediately over the malleolus) and C2 the circumference immediately upstream of each truncated cone and so on.

2) Assessment of the following symptoms with Visual Analogue Score (VAS) (1-10 points, with 10 and 1 as maximum and minimum severity of each symptom): heaviness, dysaesthesias / paraesthesias, pain; also diuresis was scored by the patient on a VAS basis.

3) Segmental multifrequency bioimpedance spectroscopy (BIS) of the edematous limb, by means of U-400® Impedimed machine, calculating the absolute figure of L-DEX (ratio between the two limbs' impedance changes, which is expressed in units).¹⁵⁻¹⁷

Complications and side effect were assessed as well, and patients were questioned on a daily basis throughout all the duration of the study.

Statistical analysis

All data were included and processed through Microsoft Excel Software for the necessary calculations and the statistical analysis; results were expressed, where necessary, as mean and standard deviation (SD).

Results

All the eight patients completed the scheduled treatment, without any violation from the protocol.

The pre-treatment average volume of the whole pathologic limb was 9462,85 (SD±3407,02) cc, while the lower leg volume had a mean volume of 4055,52 cc (SD±1539,35). After the treatment the mean volume of the whole limb decreased to 9297,37 cc (SD±3393,20), which accounts for a 165,48 cc (2%) reduction after 6 days of physiotherapist +/- self administered therapy.

The VAS assessment for each symptom and as overall measurements highlighted a significant improvement (score decrease) and detailed data are listed in Table II.

Diuresis was reported by the patients as significantly and progressively increased throughout the therapeutic cycle, and more in details diuresis VAS measurement passed from a mean value of 7.43 ± 1.81 to 8.57 ± 0.98 (15% increase).

The overall pre-treatment L-DEX value was 10,01 units (SD±8.99) for the edematous limb, while the

TABLE II.—*Symptoms.*

	SYMPTOM (mean value and S.D.) Pretreatment	Post-treatment	Reduction (%)
Heaviness	4.57±3.46	2.43±2.57	-47%
Paraesthesias (Dysesthesias)	1.71±2.63	0.71±1.50	-58%
Pain	1.57±2.57	0.57±0.79	-64%

separate analysis of L-DEX in LYM and LIP limbs highlighted values of 13.28 ± 8.15 and 1.85 ± 5.73 respectively. After the six-days treatment, fluid retention decreased in all patients. More in detail the post-therapy BIS measurements showed an overall decrease of the cumulative L-DEX, which resulted to be 793 (SD±11.25) in LYM+LIP patients; the average L-DEX percentage reduction was 21%, which accounts for a significant reduction of the fluid amount in the intercellular space. Interestingly the LYM limbs presented a post-treatment L-DEX value of 10.94 ± 12.05 which corresponds to a 18% decrease, while the LIP limbs showed a 0.40 ± 4.38 final L-DEX, corresponding to 78% decrease.

Side effects were not reported by patients throughout the pilot study and in the following 4 weeks.

All the patients have shown a high compliance with the treatment, learning quickly and adequately the methodology to apply the device on the edematous limb/s at home on a daily basis.

Discussion

LYM and LIP represent complex, mostly chronic diseases which often tend to recur and worsen along the time. Whichever treatment of these two diseases is of multifaceted nature, with compression as the cornerstone therapy. Past electro-medical devices have proved to be of some utility in LYM and LIP treatment, though sound data are still lacking. The application of Trasponder® in this group of patients has resulted in some improvement in terms of edema and symptoms, both from the clinical and from the instrumental point of view. Among symptoms, pain basal value was quite low, which is expected in LYM especially, hence the action of the device on this symptom should not be overemphasized. Efficacy and safety of this electromedical device has been demonstrated in the present preliminary study, which was based on a very short duration protocol and on a very small

group of patients. Also, noticeably, two/third of the treatment was self-administered by the patient through a domiciliary regimen.

It is acknowledged here that a larger cohort of patients, combined with a longer treatment period would be needed before drawing any significant conclusion. Similarly a wider role of the physiotherapist could have resulted in overall better outcomes, though the easiness and reproducibility of the manual and technical methodology pertinent to this device seemed to facilitate the self-administration of this treatment by the patients themselves.

Bioresonance-based technology has been proposed in LYM therapy a few years ago^{1, 6, 7} and this new device adds the possible transdermal chemical activity of active substances. Furthermore the domiciliary usage of the device widens the practical management of these patients as well.

In this preliminary experience also there was no specific safety problems. The applied microcurrents are able to interact with the body physiology,¹⁸⁻²² without significant side effects, and efficacy of bioresonance microcurrents has been shown in a few reports.¹⁸⁻²²

The bioresonance action on LYM/LIP is probably able to energise the stagnating protein aggregates (LYM is a high protein volume disease),²³ with a subsequent fragmentation and re-routing of the aggregates towards the less resistance pathways. As main consequence, this process may induce a fluid drainage, through the osmotic mechanism, combined with an activation of the lymphangion motility.²⁴ Finally also the miofibrillar activation within the smooth muscles induced by the bioresonance microcurrents has been demonstrated,⁷ which may positively impact both LYM and LIP pathophysiology. Magnesium silicate is a natural product that helps to counteract the imbalance generated by fluid retention. In fact the mixture of magnesium salts contained in the gel is able to exert high osmotic pressure and thus a chemical effect of water retrieval from the tissues towards the surface.

Conclusions

In this pilot observational study the application of different complementary technologies in one medical device has resulted in an overall improvement of main symptoms and pathologic signs of LYM and/or LIP of the lower limbs.

More in details bioresonance induced by microcurrents, together with the transdermal channelling of active principles may achieve the synergetic effect to reduce the edematous component of LYM and LIP, with possible improvements in the loco-regional tissue metabolism.

The present preliminary experience provided data on efficacy and safety of this technology in a very small group of patients and at very short-term follow-up. Good patients' compliance to the protocol has been highlighted and the possibility of self-administration of this medical device on the affected tissues represent an interesting option as well.

Larger series and longer duration protocols are necessary to assess and validate this combined technology medical device. Longer follow-up data are also expected to complement these very preliminary data, as well as to assess recurrence rate, though Trasponder® showed an overall promising degree of efficacy and a good safety profile in our limited observational study.

Riassunto

Applicazione di microcorrenti di biorisonanza e veicolazione transdermica di principi attivi nel linfedema e lipedema degli arti inferiori: studio pilota

Obiettivo. L'applicazione di microcorrenti di biorisonanza può permettere la lisi degli aggregati proteici ed un conseguente aumento del drenaggio linfatico. Combinando la biorisonanza con il passaggio di principi attivi, mediante una elettroporazione transdermica, è possibile attivare teoricamente la microcircolazione e la clearance del tessuto connettivo. È stato condotto uno studio pilota con un apparecchio elettro-medicale, che include queste due tecnologie (Trasponder®), su pazienti affetti da linfedema (LYM) e/o lipedema (LIP) degli arti inferiori.

Metodi. Otto pazienti affetti da LYM monolaterale primario o secondario o da LIP sono stati sottoposti a sei sedute giornaliere consecutive con il dispositivo; le prime due sessioni sono state effettuate da un fisioterapista, mentre le successive quattro sono state auto-somministrate dal paziente stesso a domicilio (dopo essere stato istruito sull'utilizzo). Nel corso di ogni sessione è stato veicola-

to Silicato di Magnesio per via transcutanea. Le indagini condotte pre- e post-trattamento sono state le seguenti: 1) volumetria degli arti inferiori mediante rilevazione centimetrica; 2) analisi bioimpedenziometrica distrettuale per lo studio del cambiamento dei fluidi, con indice L-DEX; 3) valutazione mediante scala visiva analogica (VAS) (punteggio 0-10) per i sintomi correlati.

Risultati. Tutti i pazienti hanno portato a termine il protocollo. Dopo il trattamento il volume medio di ogni arto si è ridotto da 9462,85 (DS±3407,02) a 9297,37 cc (DS±3393,20), con una riduzione di 165,48 cc (2%) dopo sei giorni di trattamento. I sintomi rilevati con scala VAS si sono modificati nel seguente modo: pesantezza da 4,57±3,46 a 2,43±2,57 (- 47%), disestesie da 1,71±2,63 a 0,71±1,50 (- 58%), dolore da 1,57±2,57 a 0,57±0,79 (- 64%). La valutazione della diuresi con VAS è passata da 7,43±1,81 a 8,57±0,98 (incremento del 15%). La riduzione media dell'indice L-DEX è stata del 21%. Non è stato riportato alcun effetto collaterale ed è stata rilevata una buona compliance da parte dei pazienti.

Conclusioni. I dati preliminari di questo studio pilota mostrano che la combinazione di microcorrenti di biorisonanza con veicolazione transdermica di principi attivi potrebbe risultare in una riduzione dell'edema ed in un miglioramento dei sintomi nei pazienti affetti da LYM o LIP degli arti inferiori. L'auto-somministrazione dell'elettromedicale è risultata possibile ed efficace; non è stato riportato alcun effetto collaterale.

PAROLE CHIAVE: Linfedema - Estremità inferiori - Somministrazione cutanea.

References

1. Cavezzi A, Michelini S. Phlebolympheoedema: from diagnosis to therapy. Bologna: PR Communications Ed.; 1998.
2. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010;87:198-210.
3. Casley-Smith JR. Benzopyrones in the treatment of lymphoedema. Int Angiol 1999;18:31-41.
4. Casley-Smith JR. Modern treatment for lymphoedema. Adelaide: L.A.A. Ed.; 1997.
5. ISL, Executive Committee. The diagnosis and treatment of peripheral lymphoedema. Consensus Document. Lymphology 1995;28:113-7.
6. Cavezzi A, Cavezzi P, Indignozzi I, Corsi R, Jakubiak I. Trattamento globale integrato intensivo, con ricovero breve, del linfedema degli arti inferiori: studio clinico-strumentale. Linfologia 2001;5:20-5.
7. Ricci M, Paladini S: Demonstration of Flowave's effectiveness through lymphoscintigraphy. EJLRP 2006;16:14-8.
8. Ohkuma M. Treatment of peripheral lymphedema by concomitant application of magnetic fields, vibration and hyperthermia: a preliminary report. Lymphology 2002;35:87-90.
9. Belmonte R, Tejero M, Ferrer M, Muniesa JM, Duarte E, Cunillera O, Escalada F. Efficacy of low-frequency low-intensity electrotherapy in the treatment of breast cancer-related lymphoedema: a cross-over randomized trial. Clin Rehabil 2012;26:607-18.
10. Langendoen SI, Habbema L, Nijsten, Neumann HA. Lipoedema: from clinical presentation to therapy. A review of the literature Br J Dermatol 2009;161:980-6.

11. Schmeller W, Hueppe M, Meier-Vollrath I. Tumescant liposuction in lipoedema yields good long-term results. *Br J Dermatol* 2012;166:161-8.
12. Warren Peled A, Slavin SA, Brorson H. Long-term outcome after surgical treatment of lipoedema. *Ann Plast Surg* 2012;68:303-7.
13. Ricci M, Paladini S. Demonstration of Flowave's effectiveness through lymphoscintigraphy. *EJLRP* 2006;49:14-8.
14. Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Revilla-Vázquez AL. Electroporation as an efficient physical enhancer for skin drug delivery. *J Clin Pharmacol* 2009;49:1262-83.
15. Cavezzi A, Schingale F, Elio C. Limb volume measurement: from the past methods to optoelectronic technologies, bioimpedance analysis and laser based devices. *Int Angiol* 2010;29:392-4.
16. Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, York S, Kilbreath SL. Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. *Cancer Invest* 2010;28:54-62.
17. Ward LC, Czerniec S, Kilbreath SL. Operational equivalence of bioimpedance indices and perometry for the assessment of unilateral arm lymphedema. *Lymphat Res Biol* 2009;7:81-5.
18. Cook Morales M, LaRosa E et al. Effects of electrical stimulation on lymphatic flow and limb volume in the rat. *Phys Ther* 1994;74:1040-6.
19. Adey WR. Physiological signalling across cell membranes and cooperative influences of extremely low frequency electromagnetic fields. In: Frohlich H, editor. *Biological coherence and response to external stimuli*. Berlin-Heidelberg: Springer-Verlag; 1988. p. 148-70.
20. Carey LC. Effect of continuous directelectric current on healing wounds. *Surgical Forum* 1962;13:33-5.
21. Franzeck U, Spiegel I, Fischer M, Börtzler C, Stahel HU, Bollinger A. Combined physical therapy for lymphedema evaluated by fluorescence microlymphography and lymph capillary measurements. *J Vasc Res* 1997;34:306-11.
22. Reed BV. Effects of high voltage pulsed electrical stimulation on microvascular permeability to plasma proteins. *Phys Ther* 1988;68:491-5.
23. Olszewski WL. Pathophysiological aspects of lymphedema of human limbs: Lymph protein composition. *Lymphat Res Biol* 2003;1:235-43.
24. Schmid-Schonbein GW. Microlymphatics and lymph Flow. *Physiological Rev* 1990;70:987-1027.
25. Colombo P, Catellani PL, Gazzaniga A, Menegatti E, Vidale E. *Principi di Tecnologie Farmaceutiche*. Milan: Casa Editrice Ambrosiana; 2004.

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