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EUROPEAN SOCIETY FOR VASCULAR SURGERY - 5TH DECEMBER 2009, OSLO (NOR)

62^{ES} JOURNÉES INTERNATIONALES FRANCOPHONES D'ANGÉIOLOGIE - 8-9TH JANUARY 2010, PARIS (FR)

CONTROVERSIES AND UPDATE IN VASCULAR SURGERY 2010 - 22-23TH JANUARY 2010, PARIS (FR)

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BIOMECHANICAL STUDY OF THE GAIT IN PATIENTS WITH LOWER LIMB LYMPHEDEMA

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ABSTRACT

Introduction: The increase of the leg mass due to the lymphedema has several implications on the biomechanics of gait. Human gait can be roughly divided in two phases: stance and swing, depending on the activity of each leg. During stance, the limb is on the ground and must support the body weight while the contralateral limb swings forward to achieve a step. We hypothesize that the increase in the mass of the affected leg will cause difficulties in the swing phase. The step would be shorter and would impact with the ground with higher forces both vertical and horizontal (braking). In addition, it is expected that gait would be asymmetric with shorter steps in the affected leg.

Material and Methods: We conducted a pilot study to evaluate gait abnormalities in two patients with unilateral and bilateral lymphedema. The patients walked on a force plate of the system NED/IBV AMH (IBV, Valencia Spain) while the ground reaction forces (GRF) under their feet were recorded and analysed.

Results and Discussion:

Unilateral Lymphedema: The vertical forces were larger in the non-affected leg, while the horizontal braking forces were bigger in the affected leg suggesting a gait compensation mechanism by the non-affected side.

Bilateral Lymphedema: Gait was slow and the vertical GRF pattern was flat, not showing the typical 2-peak shape. This might indicate flat foot with reduced ankle mobility or a mechanism to minimize the excessive loads at weight-bearing and take-off caused by the large weight of the patient. Finally, the large medio-lateral forces found, suggest gait stability problems.

Conclusion: These patients showed larger ground reaction forces with abnormal patterns, including compensation with the unaffected leg. This might cause biomechanical complications related to osteoarthritis or falls (lack of stability during gait) affecting severely the quality of life. Further research including measurements of the body kinematics is guaranteed.

KEY WORDS: lymphoedema, biomechanics, gait, force plate, kinematics' analysis.

INTRODUCTION

Normal Human Gait

The human gait is the most characteristic way of locomotion and it is defined as a quasi-cyclical movement with sequential alternative stance of one foot or both^{1,2}.

This periodic leg movement is the essence of the cyclic nature of human gait.

The gait cycle is usually defined between consecutive floor contacts of the same leg. There are two main phases in the gait cycle, during stance phase, the ipsilateral foot is on the ground, whereas in the swing phase the leg advances forward preparation for the next contact of the foot with the ground, also named foot strike.

There are three parts in the stance phase: first double support, when both feet are in contact with the ground and the ipsilateral foot more advanced. Second, the single limb stance, when the contralateral foot is swinging through and only the ipsilateral foot is on the ground. Finally, the second double support, when both feet are again in ground with the contralateral foot more advanced. During the gait cycle there are several functional periods, five during stance phase and three during swing. The names of these events are self-descriptive and are based on the movement of the foot and on their functional relevance:

1. Foot ground contact or heel strike. Initiates the gait cycle and represents the point at which the body's centre of gravity is at its lowest position. The limb must accept the body weight and damp the impact with the ground. The ankle is dorsiflexed while the knee is extended and flexes slightly to accept the weight smoothly.
2. Foot-flat is the time when the plantar surface of the foot touches the ground.
3. Midstance occurs when the swinging (contralateral) foot passes the stance foot and the body's centre of gravity is at its highest position.

4. Heel-off occurs as the heel loses contact with the ground and pushoff is initiated via the triceps surae muscles, which plantar flexes the ankle. Simultaneously, the contralateral foot contacts the ground.
5. Toe-off terminates the stance phase as the foot leaves the ground.

In the swing phase the goal is to advance forward the leg while the contralateral leg supports the body weight. It is necessary to provide foot clearance avoiding that the foot contacts the ground. The phases considered are as follows:

6. Acceleration begins as soon as the foot leaves the ground. The subject activates the hip flexor muscles to accelerate the leg forward with the knee flexed.
7. Midswing occurs when the foot passes directly beneath the body, coincidental with midstance for the other foot. The ankle dorsiflexes to obtain foot clearance, because at this point the foot passes at its lower point with respect to the ground.
8. Deceleration describes the action of the muscles as they slow the leg and stabilize the foot in preparation for the next heel strike.

Lymphedema and Locomotion Disorders

Lymphedema is the swelling of a body part, usually arms or legs, due to the accumulation of lymph fluid. This is a chronic, progressive condition that requires specific management for a lifetime and has several complications from a biomechanical point of view that did not receive much attention.

Although gait problems have been reported in patients with lower limb lymphedema³, the changes in their pattern by gait analysis have not been documented yet. In the literature, the orthopaedic problems related to lymphedema have been barely addressed. A poor mobility leads to oedema and which, in turn, impairs the range of motion of the joints. Oedema, particularly of the leg, restricts the motion of hip, knee and ankle joints, possibly affecting the gait pattern. Comprehension of the orthopaedic findings should therefore be considered in the diagnosis and treatment of lymphedema⁴.

Gait can be affected by lymphedema, and a proper gait was the best determining factor of quality of life and limb function⁵. From a biomechanical point of view, the increase in the mass of the affected limb might cause difficulties in the swing phase of gait. It is also possible that there is a decrease in the range of motion of the ankle, knee or hip joints. These conditions might cause different gait compensation mechanisms.

OBJECTIVES

The increase of the leg mass due to the lymphedema has several implications on the biomechanics of gait. We hypothesize that the increase in the mass of the affected leg will cause difficulties in the swing phase. The step would be shorter and would impact with the ground with higher forces both vertical and horizontal (braking). In addition, it is expected that gait would be asymmetric with shorter steps in the affected leg in the case of patients with

unilateral lymphedema. These disturbances are also expected to cause modifications in the motion of other body parts such as the trunk or the non-affected leg.

MATERIAL AND METHODS

We conducted a pilot study to evaluate gait abnormalities in three patients: one with moderate and one with severe unilateral lymphedema, and one patient with bilateral lymphedema. The patients walked on a force plate of the system NED/IBV AMH (IBV, Valencia Spain) while the ground reaction forces (GRF) under each foot were recorded in consecutive walking trials. A minimum of 5 correct foot contacts were retained for analysis. Gait can be analysed using different methods, which measure different aspects of the movement, independently or simultaneously. Motion-analysis methods can be used to measure the movement patterns, as the joint angles, generated during gait. Kinetic methods are those that measure and analyse the forces produced during gait, usually the ground reaction forces (GRF) that are the forces produced by the body on the supporting surface. The muscular activity generated during walking can also be recorded by means of electromyographic methods⁶.

The ground reaction forces (GRF) are the forces between the foot and the supporting surface; they are related to the acceleration of the total body centre of mass. There exist different types of force platforms that are fixed on the ground and measure the GRF, which are three-dimensional: there are forces in the antero-posterior, medio-lateral and vertical axes of the body. Other devices, such as the plantar pressure insoles only record the vertical component of the forces, although in combination with other methods they can be used to estimate the complete GRF⁷. The vertical component of the GRF is the one with the largest magnitude because it depends on the weight of the subject, which is the mass multiplied by the gravity, e.g. a mass of 90 Kg by the acceleration due to gravity 9,81 m/s² would result in a weight (force) of 882.9 N. The typical pattern of the vertical GRF is a curve with two peaks and one valley in between (see figure 1). The first peak is related to the foot contact and weight acceptance while the second is related to the push-off. These peaks correspond to the double support phases and they are larger than the weight of the subject. The valley between these peaks corresponds to the single support phase and its magnitude is approximately the body weight. The antero-posterior forces, due to friction, are initially indicating a decelerating force during the foot contact, then decrease to zero during single support and goes to positive values during the second double-support. Therefore, it contributes to a forward acceleration of the body before the foot leaves the ground. The medio-lateral component of the force is related to the lateral deviations of the foot and the accelerations of the body centre of mass in this axis. In this respect, larger medio-lateral forces indicate a lower stability and efficiency of gait. It is less stable because the center of mass is accelerated medio-laterally, for instance with large trunk oscillations in the frontal plane, making the person more prone to fall sideways. The patterns of the three components of the GRF are analysed considering the hypotheses formulated about the potential gait disturbances of patients with lymphedema in the lower limb.

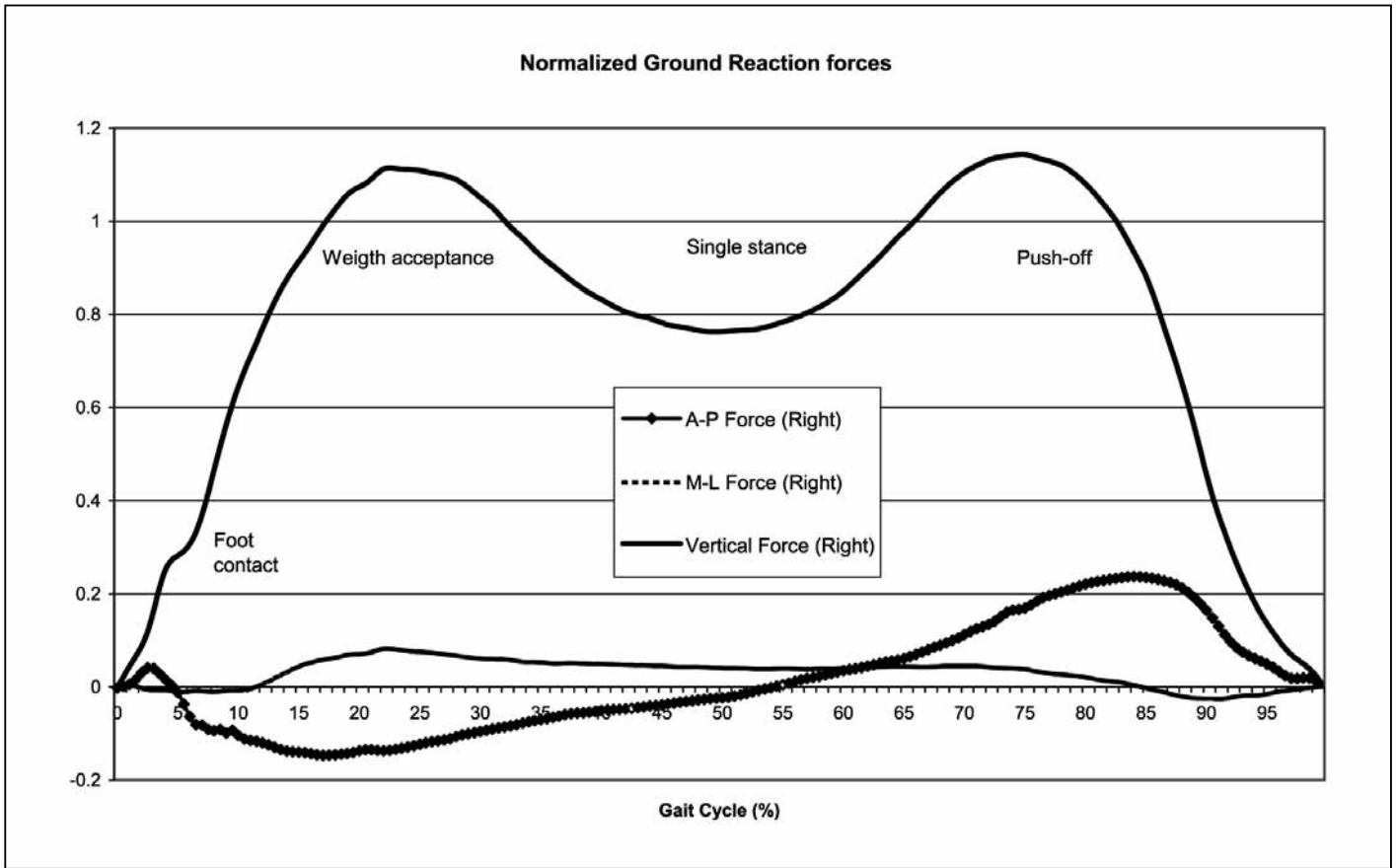


Fig. 1 - Pattern of ground reaction forces (GRF), including vertical, medio-lateral (M-L) and antero-posterior (A-P) force components, from a normal healthy subject.

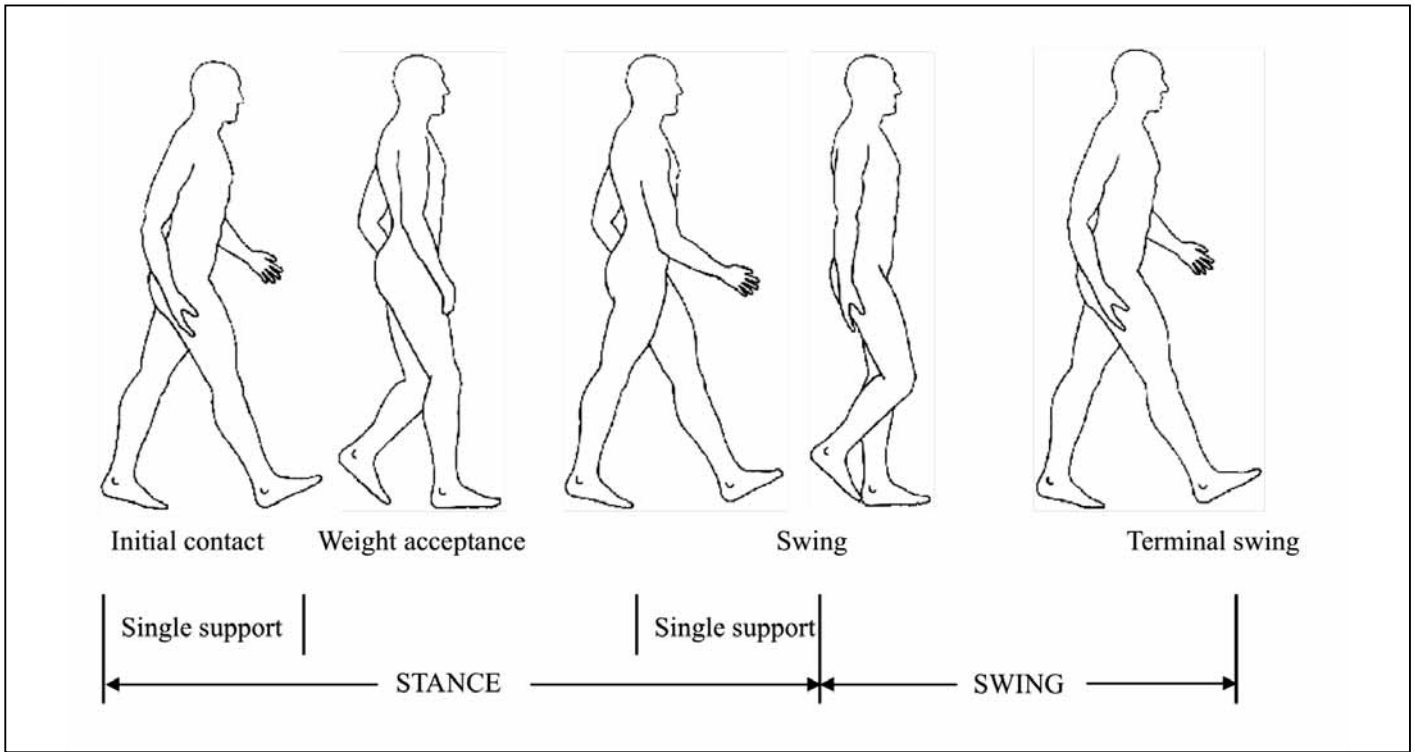


Fig. 2 - Scheme of the gait cycle and its phases.

RESULTS

Unilateral Lymphedema

The patient 1 is a 46 years-old man with a moderate unilateral lower limb lymphedema in a Klippel-Trenaunay syndrome. He presented a chronic lymphedema in stage III that appeared at 14 years-old and has not been treated for all these years. The lymphoscintigraphic study showed an aplasia of lymphatics in right limb. After the treatment with Decongestive Physical therapy, the volume of his affected limb was 11684 ml and the contralateral was 8695 ml, so the oedema was 3089 ml. Today, he is compliant with flat knit, class II hosiery, exercises and skin care. The analysis of the ground reaction forces measured during gait showed that the vertical forces were larger in the non-affected leg, while the horizontal braking forces were bigger in the affected leg suggesting a gait compensation mechanism by the non-affected side.

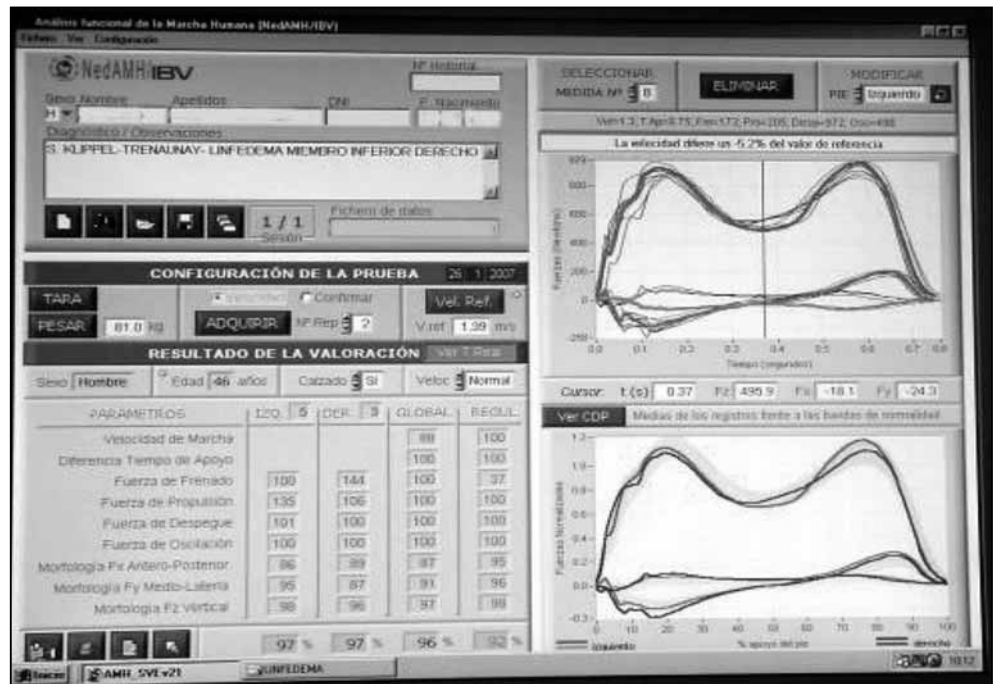


Fig. 3 - Screen capture of the data recording program showing the measurements on a walking trial of a patient suffering a unilateral lymphedema. The upper graph shows the individual recorded forces across time, while the lower one shows the forces across gait cycle percentage, averaged and normalized with respect to body weight.

Unilateral Elephantiasic Lymphedema

The patient 2 is a 48-years-old woman, affected by a chronic late stage III unilateral lymphedema. She started with the symptoms 25 years ago, presenting swelling in the right lower limb and had never received any treatment for lymphedema. She has suffered more than 20 attacks of lymphangitis that have been treated with non-steroidal anti-inflammatory drugs and sometimes with penicillin. She is attending the Unit for the first time in January 2007, presenting an elephantiasic lymphedema with a volume of 22,223 ml and an oedema (difference between limbs) was 7850 ml, and in the skin many complications as dermatofibrosclerosis,

papilomatosis, lymph cysts and hyperkeratosis.

A detailed analysis of the ground reaction forces reveals interesting patterns. With respect to the antero-posterior forces both legs show high degree symmetry, the curves of the right and left legs are very similar. However these forces are relatively small, indicating a slow non-brisk gait. (see figure 4a) The Medio-lateral forces are related to gait stability. As they directed to the median plane of the body left and right have opposite directions (that is why one is positive and the other negative). These forces are not symmetric, there are larger forces in the right leg, which is the affected one. This indicates a gait pattern with large inclinations of the trunk (see figure 4b).

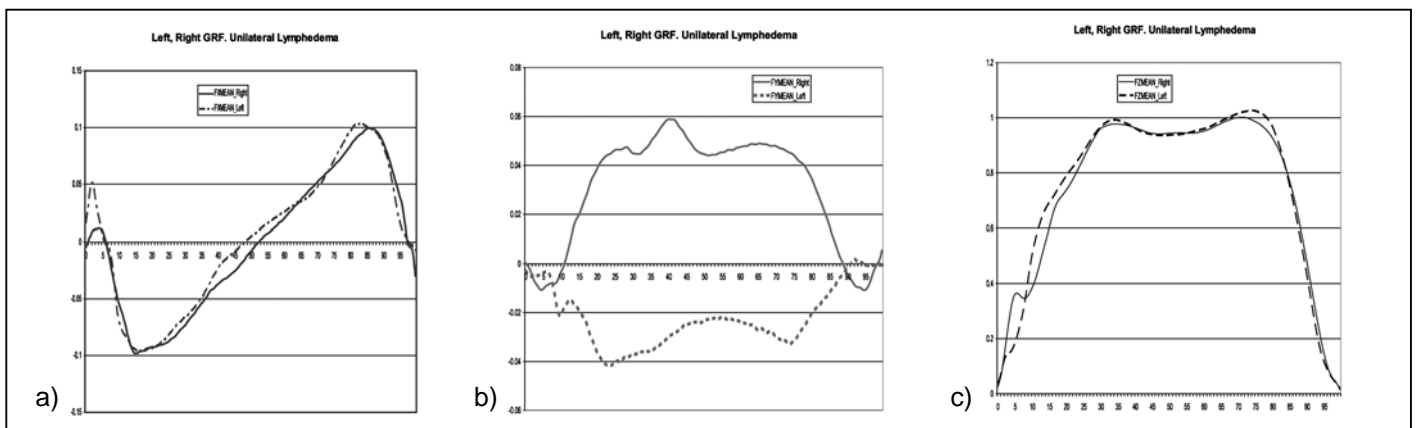


Fig. 4 - Averaged ground reaction force patterns normalized to body weight and plotted with respect to gait cycle percentage of a patient suffering a unilateral elephantiasic lymphedema. From left to right: a) Antero-posterior (A-P) forces; b) Medio-lateral forces and c) Vertical ground reaction forces.

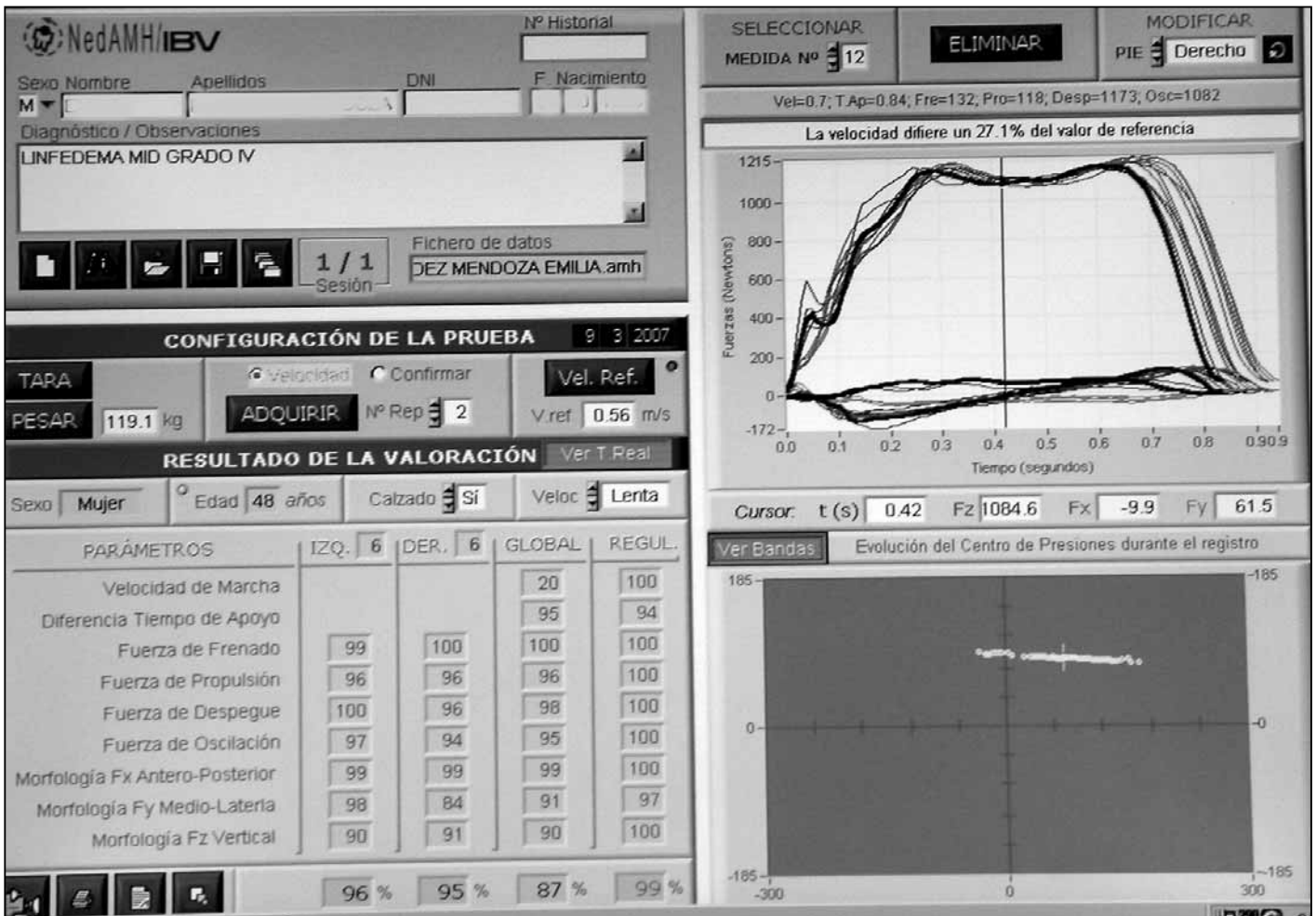


Fig. 5 - Biomechanical analysis of the gait in a unilateral elephantiasis, with the system NED/IBV AMH (IBV, Valencia Spain).

The vertical ground reaction forces are very symmetric between the right and left leg. This indicates that there are compensatory mechanisms of gait. The affected leg shows an impulsive load during heel contact due to the high weight of the leg. This is reflected in the peak of the vertical force loading. It must be noted that the curve is not as “flat” as in the bilateral case, but the valley occurring during single stance is not as pronounced as in the normal cases. This suggests that, like in the bilateral patients, the steps are of relatively short length with prolonged double stance phases.

Bilateral Lymphedema

The patient 3 is a 53-years-old woman, with a chronic lipolymphedema, that started at pregnancy 32 years ago. Both limbs are affected with a stage III lymphedema, with a volume of 14,759 ml for left lower limb and 14,090 ml for right lower limb. Joint mobility is impaired due to the swelling and osteoarthritis of hips and knees (Figure 6).

Gait was slow and the vertical GRF pattern was flat in both legs, not showing the typical 2-peak shape (Figure 7). This might indicate flat foot with reduced ankle mobility. It is unclear if the mobility of the ankle is reduced due to the oedema or it is

mechanism to minimize the excessive loads at weight-bearing and take-off caused by the large weight of the patient. In addition, as a mechanism to minimise the GRF the patient walked very slowly. Finally, the large medio-lateral forces found, suggest gait stability problems. It must be noted that there was a larger braking force with the right leg.



Fig. 6 - Patient suffering a bilateral lipo-lymphedema

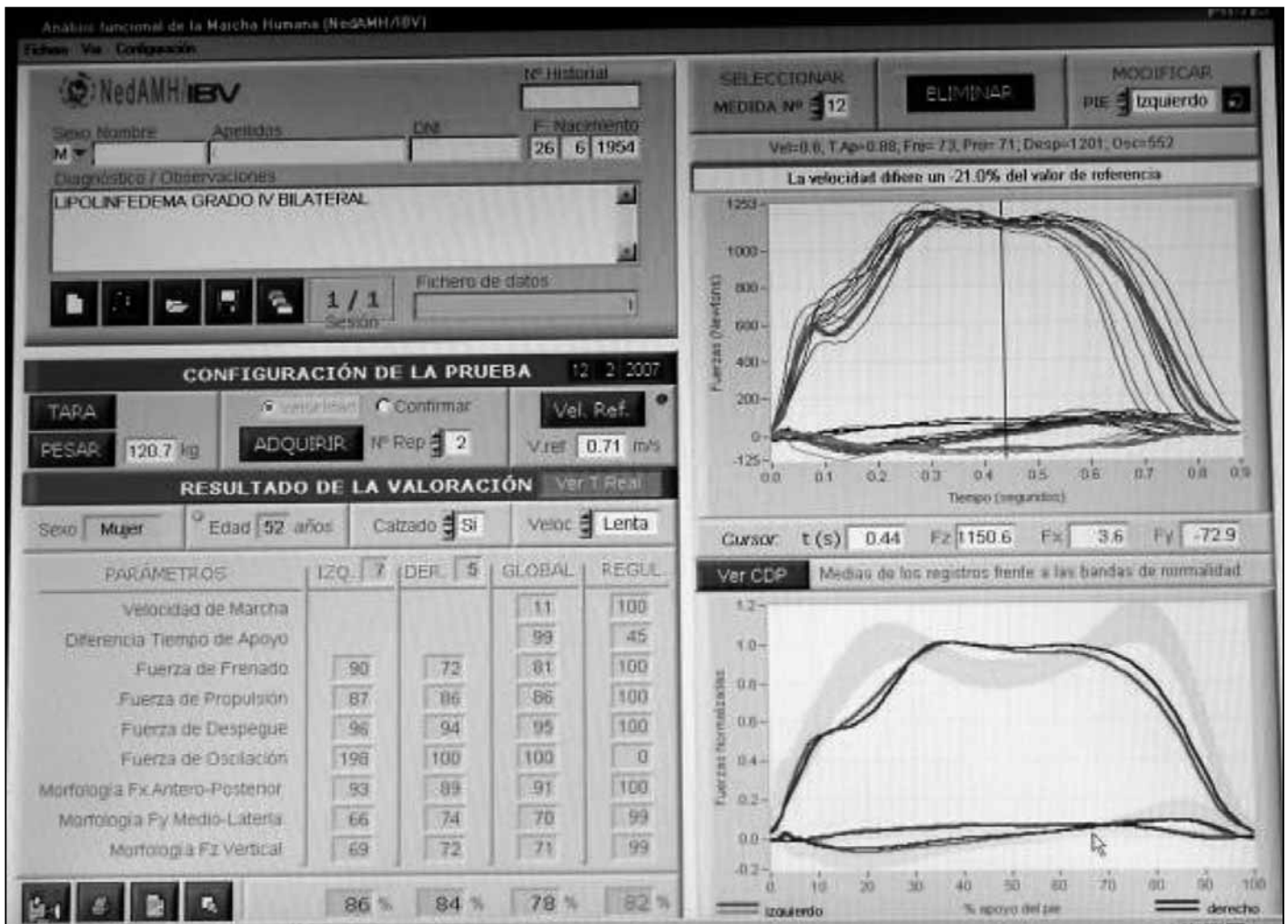


Fig. 7 - Screen capture of the data recording program showing the measurements on a walking trial of a patient suffering a bilateral lymphedema. The upper graph shows the individual recorded forces across time, while the lower one shows the forces across gait cycle percentage, averaged and normalized with respect to body weight.

CONCLUSIONS

Patients suffering lymphedema show clear distinctive gait patterns as reflected in the ground reaction forces during walking. An important aspect is that they show large vertical force loads with elevated rate of loading and high foot contact peaks. This is due to the large weight of the patients and, particularly, to the high weight of the limb. In addition, they show a cautious gait pattern, characterized by slow speed and short steps.

Some of the possible consequences of these ground reaction force patterns are the articular degeneration (osteoarthritis) due to large impulsive loads and, of course, the problems of stability during gait and the risk of falling. It must be mentioned that the cautious gait pattern described here has certain similarities with the idiopathic senile gait. This gait pattern is associated to the elderly older than 65 years that are at risk of falling. In this respect, it seems sensible to follow the incidence of falls in the patients with lymphedema. Falling can cause injuries such as hip fracture but also the fear of falling that affects the quality of life and self-dependency of the patient.

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UPDATE ON OXERUTIN, O-(β -HYDROXYETHYL)-RUTOSIDES FROM ESTABLISHED EVIDENCE TO RECENT FINDINGS

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ABSTRACT

Oxerutin is a phlebotrophic drug with documented effects on capillary permeability and edema, that has been used for many years in the treatment of edema, chronic venous insufficiency (CVI), and diabetic microangiopathy.

Treatment with oxerutin has been demonstrated to be effective in improving venous insufficiency symptoms, and in reducing ankle swelling and capillary filtration rate in patients with venous insufficiency and associated venous conditions. In addition, it has been shown to significantly improve microcirculation in patients with diabetic microangiopathy and neuropathy.

Studies have also demonstrated that oxerutin is very effective in improving and preserving the quality of life in patients with CVI and venous microangiopathy.

Finally, there is a large body of data confirming the safety and tolerability of long-term treatment with oxerutin.

In summary, current evidence supports the efficacy, safety, tolerability, and ease of use of oxerutin, administered both systemically and locally, in the treatment of venous disorders and other important conditions as well.

INTRODUCTION

Flavonoids have different pharmacological properties, including anti-inflammatory and antioxidant properties, which are clinically important. They facilitate vitamin C stabilization and antioxidant activity, by preventing its oxidation by copper-containing enzymes and by enhancing uptake in the liver, kidneys and adrenal glands.

The synergistic activity of these two molecules has been demonstrated by several findings: it is not an accident that the combination of bioflavonoids and vitamin C is more effective than vitamin C alone, and symptoms of bioflavonoid deficiency are closely related to those of vitamin C deficiency.

These properties have been related to the scavenger activity of flavonoids on reactive oxygen species (ROS) and on their toxic effects, and to their ability to chelate transitional metals as well. These properties appear also to be responsible for the inhibitory effect on lipoperoxidation (1).

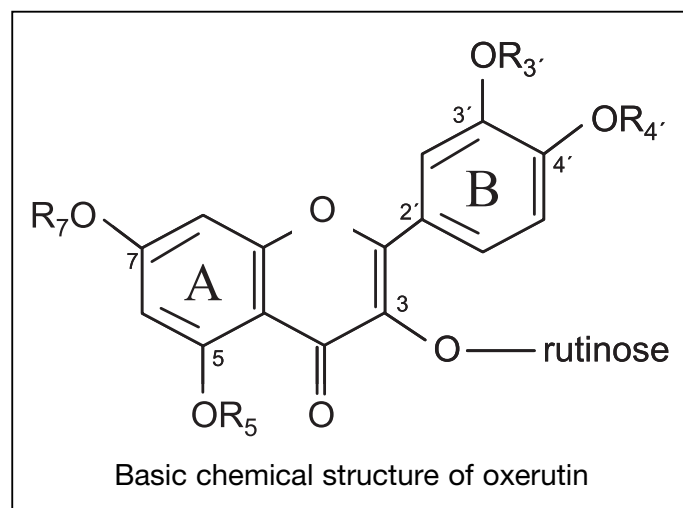
Rutosides are a standardized mixture of hydroxyethyl derivatives of rutin, a natural flavonoid that is able to protect the vascular endothelium and has a strong affinity for the venous wall (1). In

particular, rutosides exert inhibitory effects on permeability and capillary fragility (enhancing capillary resistance and platelet aggregation), reduce bleeding time, prevent alterations in blood flow and have a direct anti-inflammatory activity (1).

Most flavonoids demonstrate significant activity *in vitro* against ROS, particularly against the highly reactive hydroxyl radicals. While carrying out their antioxidant action, which increases with the increasing number of hydroxyl groups at the level of the B-ring, flavonoids are oxidized and degraded (1).

Oxerutin (see box) is a standardized mixture of mono-, di-, tri-, and tetra-hydroxyethylrutosides that has been studied for a long time for its unique biochemical and pharmacological characteristics. By exerting a predominantly inhibitory effect on micro vascular permeability, oxerutin reduce the formation of different kinds of edema which are formed in response to different types of damage, either thermal or chemical (2). This effect has been studied in humans and in animal models, and in double-blind, controlled trials conducted in healthy volunteers and in patients with chronic venous insufficiency (CVI) (2).

Diseases such as CVI or lymphatic edema are among the most frequent clinical conditions characterized by edema formation, with incompetence of the superficial venous system in association with increased hydrostatic pressure, excessive capillary distension



and increased filtration rate (3). The edema is caused by an imbalance between the amount of fluid and electrolytes leaving the bloodstream through the capillary walls to enter the interstitial space, and vice versa. In addition, during venous blood stasis local hypoxia develops, affecting physiologic characteristics of capillaries and activating endothelial cells leading to the recruitment, adhesion, and activation of granulocytes (3). Later on, fibrinogen fragments in the interstitial space increase gel matrix viscosity, affecting capillaries emptying and reinforcing the vicious circle caused by hypoxia (3).

PHARMACOLOGICAL PROPERTIES AND ANTIEDEMA ACTION OF OXERUTIN

Oxerutin exerts an inhibitory effect on capillary permeability, reducing peripheral edema typical of veno-lymphatic stasis. Under lactacidotic conditions oxerutin preserves the erythrocyte membrane deformability, modulating its flexibility, and in hypoxic veins inhibits neutrophils' and platelets' adhesion (3). Oxerutin components are also potent hydroxyl radical scavengers and can inhibit microsomal lipid peroxidation by acting on both lipoxygenase and cyclooxygenase pathways (3). Actually, flavonoids interfere with arachidonic acid metabolism by inhibiting both the enzyme responsible for its release from membranes (phospholipase A2), and other enzymes that are involved in its metabolism (cyclooxygenase-1 and 2-, 5-, and 12-lipoxygenase). In this way, they block the synthesis of important chemical mediators of inflammation such as prostaglandins, thromboxanes, and leukotrienes. This ability of flavonoids to inhibit the enzymes involved in the arachidonic cascade may be partly related to their free radical scavengers properties: in effect, by blocking oxygen radicals, these substances may inhibit lipid peroxidation phenomena, which seem to play an important role in regulating the enzymatic activity of cyclooxygenase. In this sense, the antioxidant and anti-edema properties of oxerutin improves venous tone by improving microcirculation and capillary blood flow (2).

In addition, it has been noticed for some time that the pharmacological effects of a dose of oxerutin persist at least 6 hours (3) and appear to be dose-related: actually, higher doses lead to greater effects, with faster onset of the pharmacological action without affecting its overall duration (2). For example, in a randomized, placebo-controlled, dose-ranging trial (4), variations in the capillary filtration rate (CFR) and ankle edema (EA) were evaluated in three groups of patients with venous hypertension (ambulatory venous pressure >42 mmHg) and in healthy subjects before and after a four-week treatment with different doses of oxerutin. In particular, group A (30 patients) was treated with oxerutin 500 mg tid; and group B (30 patients) with oxerutin 1 g tid; group C (30 patients) was treated with placebo; and group D (10 healthy individuals) was treated with oxerutin 1 g/day. The results showed that in group A there was a significant decrease of CFR after treatment (from a score of 7.8 to 4, $p < 0.01$); this decrease was even greater in group B (2 g/day) than that in group A (from 7.9 to 3.1, $p < 0.05$). In group C (placebo), however, there was no significant difference before or after treatment. The results of this study show that the decrease in CFR and the improvement

in signs and symptoms of edema after treatment with oxerutin are directly proportional to the dosage used in the clinical setting and thus are significantly greater with higher doses (4).

CLINICAL EFFICACY OF OXERUTIN

Oxerutin is one of the flavonoids with vasoprotective activity that is best studied and characterized, as it has been used for over 35 years for the treatment of CVI. Oxerutin, available both in gel and in oral formulation, is a phlebostrophic drug commonly used in Italy, and its pharmacodynamic effects have also been confirmed in the clinical setting: actually, treatment with oxerutin clearly improved CVI symptoms (leg fatigue, heaviness, and swelling, cramps, itching, numbness, pain on standing or in the sitting position, need to keep legs raised during the day) after only 7 days of treatment (6). Oxerutin has a strong ability to penetrate through the skin layer, and so it can directly reach the capillary wall, especially when used in the gel formulation. This type of formulation offers the advantage of a simple and convenient application, especially in older patients and in those already taking oral medications (6). Several studies have shown that oxerutin effectively affects a variety of physiopathologic mechanisms of CVI and microangiopathy, actively protecting the endothelium and the circulatory system. Several findings demonstrate that oxerutin reduce the number of circulating endothelial cells (whose increase is an important indicator of endothelial damage), the systemic and local levels of free radicals, skin flux at rest and capillary filtration rate, allowing the patient to achieve a rapid symptomatic and objective relief within a few days of treatment (7-9). Recent evidence also confirms that oxerutin therapy significantly improves the venous filling time, the transcutaneous partial pressure of oxygen (TcPo₂), and the venous capacity. In this sense, the combination of oral systemic and percutaneous topical therapy currently represents an additional benefit in the treatment of CVI and its associated problems (reduction of quality of life, disability) (6).

In a recent study carried out on 84 patients with severe CVI (ambulatory venous pressure >56 mmHg, filling time <10 sec, documented deep venous incompetence) it was demonstrated that the local efficacy of oxerutin can be increased by the application of a topical gel (10). In this study, patients were treated with 3 different treatment regimens: oral treatment with 1 g sachets of oxerutin for a total of 2g per day in combination with topical oxerutin 2% gel applied 3 times daily at the perimalleolar region; oral treatment only (at the same dosage); or light elastic compression stockings (25 mmHg at the ankle level). After 8 weeks of therapy, the improvement in skin flux, the increase in PO₂, and the decrease in pCO₂ were statistically significantly greater in the combined oral + topical treatment group (Figures 1 and 2). Oxerutin treatment was well tolerated by all patients, without any adverse events or compliance issues throughout the study (10).

These results were also confirmed in a long term setting, in a prospective comparative study analyzing the data from a clinical registry including 400 patients with venous hypertension and diabetic microangiopathy, followed-up for 5 years (11). To allow an in-depth assessment of diabetic microangiopathy, patients were divided into 4 groups. In group A (98 patients) there were included

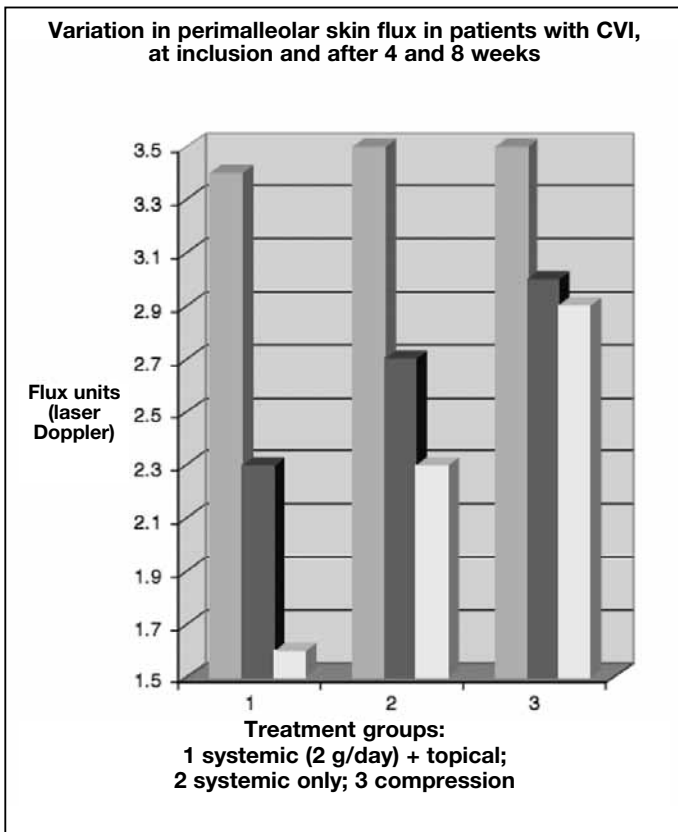


Fig. 1 - Variations in skin flux in the 3 treatment groups (oral treatment with 1 g sachets of oxerutin +2% topical gel, oral treatment alone, or use of elastic compression stockings). A significantly increased skin flux was associated with severe CVI and venous microangiopathy. The decrease in skin flux was more evident after the combined oral and topical treatment. Taken from (10).

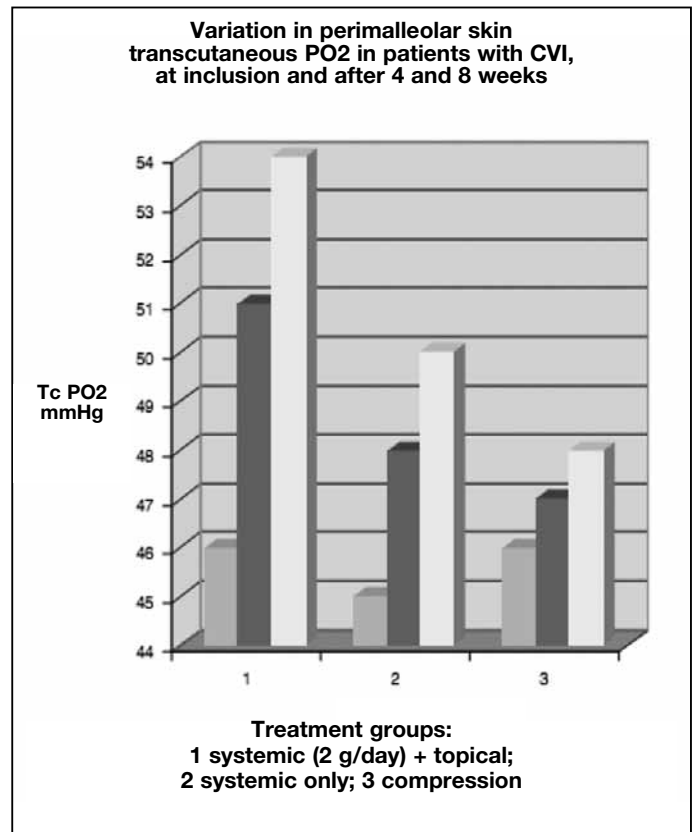


Fig. 2 - Transcutaneous PO2 changes in the 3 treatment groups (oral treatment with 1 g sachets of oxerutin +2% topical gel, oral treatment alone, or use of elastic compression stockings). In CVI and microangiopathy, PO2 is decreased and pCO2 tends to increase, particularly at the level of internal perimalleolare region. The increase in PO2 was significantly higher after the combined oral and topical treatment. Taken from (10).

patients with CVI but without diabetes mellitus, treated with 500-mg tablets of oxerutin 3 times daily; group B (87 patients) included cases of CVI with diabetes mellitus, treated with 1-g sachets of oxerutin twice daily; group C included 90 subjects (including 42 with diabetes mellitus) used as controls, who did not receive any form of treatment; and group D consisted of 113 patients (of whom 42 with diabetes mellitus), treated with elastic compression stockings providing a 25-mmHg ankle pressure. In this study, the venoprotective effect of oxerutin in the prevention of chronic complications such as venous ulcers was estimated by evaluating edema and the capillary filtration rate (CFR) in association with a clinical score scale. The results showed that, after 5 years of therapy, treatment with oxerutin significantly reduced edema, swelling, and the CFR compared to controls and patients treated with elastic compression stockings (Table 1). Venous ulcers were also significantly increased in the groups not treated with oxerutin. These important findings are the first evidence of oxerutin efficacy in the long-term treatment of edema and venous hypertension, and in the prevention of deterioration of the distal venous system in a particular population of patients at higher risk of developing microangiopathy such as those with diabetes (11).

ROLE IN HYPERTENSIVE AND DIABETIC MICROANGIOPATHY

All the above findings suggest that, thanks to its characteristics, oxerutin offers a new therapeutic option for all aspects of CVI. For example, in a study performed on 60 patients with severe venous hypertension due to CVI, with ankle swelling and lipodermatosclerosis, oral treatment with oxerutin at a dosage of 2 g per day for 8 weeks resulted in a significant reduction in resting skin flux and a significant improvement in ankle swelling compared to placebo ($p < 0.05$). The decrease in capillary filtration rate was also associated with a significantly better improvement in signs and symptoms of CVI ($p < 0.05$) (12). Treatment with oxerutin can also improve microcirculation in patients with diabetic microangiopathy and neuropathy (13). In a study conducted in healthy volunteers and in patients with diabetic microangiopathy, with or without neuropathy, treated with oxerutin 1g bid for 6 months, significant reductions in resting skin flux and in capillary filtration rate were observed compared to placebo ($p < 0.05$). A significant increase in venoarteriolar response – which represents an important mechanism of vascular autoregulation in response to changes in venous pressure – was also observed in the

active treatment groups. These improvements were even greater in diabetic patients with microangiopathy but without neuropathy (Table 2). These findings support the efficacy of oxerutin in reducing capillary filtration rate and edema, as well as its important contributions to symptoms' improvement. This is especially important in diabetic patients, where phlebotropic therapies can slow the progression of neuropathy – which is strongly affected by

edematous states – and prevent the progression of microangiopathy from early stage to clinical disease (11).

OXERUTIN AND QUALITY OF LIFE

CVI is a highly disabling condition that can significantly impair the quality of life of patients, who could experience a partial loss

Table 1 - Capillary Filtration Rate (CFR) and Analogue Scale Line (ASL) score. Taken from (11).

Variable	Study group			
	A	B	C	D
Basal				
CFR, ml/min/100 cm³ of tissue				
Group	2.3	2.2	2.2	2.2
DM patients	2.3	2.2	2.3
ASL score				
Group	34	33	36	35
DM patients	36	37	37
Total cholesterol, mg/dl				
Group	234	239	231	219
DM patients	244	242	234
2 years				
CFR, ml/min/100 cm³ of tissue	1.8 ^b	1.7 ^b	1.9	1.9
ASL score	21 ^b	20 ^b	30	33
Total cholesterol, mg/dl	197 ^b	198 ^b	212 ^b	215
5 years				
CFR, ml/min/100 cm³ of tissue				
Group	1.6 ^{b,c}	1.6 ^{b,c}	1.9	1.9
DM patients	1.6 ^{b,c}	2.0	2.1 ^b
ASL score				
Group	22 ^{b,c}	19 ^{b,c}	32	33
DM patients	22 ^b	34	36
Total cholesterol, mg/dl				
Group	198 ^{b,c}	187 ^{b,c}	221	218
DM patients	198 ^{b,c}	206 ^b	223 ^b

a: Data are expressed as mean. b: P < 0.05. c: P < 0.05 versus C and D groups. See the text for the definition of the treatments in the study groups.

Table 2 - Results of 6-month treatment with oxerutin in healthy volunteers (A) and in patients with diabetic microangiopathy, with (B) or without (C) neuropathy. Taken from (13)).

		Inclusion			After 6 Months		
		RF*	VAR†	RAS	Rf	VAR	RAS
A	Treatment	3.4 (1.1)	21 (11-56)	2.5 (0.3)	2.1 (0.3)‡	29 (12-66)‡	1.8 (0.2)
	Placebo	3.3 (1)	22 (14-58)	2.4 (0.3)	3.2 (0.4)	18 (8-44)	2.3 (0.3)
B	Treatment	2.2 (0.5)	31 (18-66)	2.1 (0.2)	1.7 (0.2)‡	38 (13-55)	1.7 (0.2)
	Placebo	2.2 (0.6)	32 (19-58)	2.2 (0.2)	2.3 (0.5)	33 (12-50)‡	2.22 (0.3)‡
C	Treatment	1.2 (0.2)	46 (33-75)	1.9 (0.2)	1.3 (0.2)	45 (34-67)	1.8 (0.1)
	Placebo	1.2 (0.2)	46 (32-74)	1.8 (0.2)	1.2 (0.2)	46 (34-65)	1.9 (0.1)

The data are expressed as mean (SD). *Resting flux (RF) in flux units; †venoarteriolar response (VAR) (median and range), and mean (SD) using an extensimeter; ‡rate of ankle swelling (RAS) (in ml/min per 100 g of tissue, per minute) at inclusion and after 6 months of treatment. §P < 0.05.

of autonomy and severe functional limitations with the progression of the disease.

Some studies have shown that the effect of oxerutin therapy is not limited to improvements in edema and microcirculation, but it also preserve patient's functioning, ensuring a better venous-related quality of life.

An interesting investigation of this aspect was carried out in one study (14) which estimated the efficacy of oxerutin using the Venous Quality of Life Score (Ve-QOL), a score specifically used to assess, in a simplified way, changes in the quality of life in patients with venous disease and particularly in those with CVI. In the first part of the study, a group of 46 patients with severe venous hypertension (CVI and ankle swelling) was treated with oxerutin 2 g/day for 8 weeks, while a second group of 62 patients with similar characteristics was included in a register where the same treatment protocol was applied with a further reassessment after 8 weeks.

Using the Ve-QOL questionnaire, it was found that the treatment with oxerutin lead to a significant reduction (that is improvement) in the scores after 4 weeks of treatment, from a score of 85 to 61. These results were maintained after 8 weeks of treatment, with a further reduction in Ve-QOL scores (46.8% of the initial value, $p < 0.05$) (Figure 3).

The results of this study demonstrate that treatment with oral oxerutin is effective and fast-acting in improving not only the microcirculation, but also the quality of life in patients with CVI and venous microangiopathy, with a high skin flux, a high

capillary filtration rate and ankle edema, whereas the effects of diosmin + hesperidin seem somewhat limited. Importantly, these findings confirm the role of oxerutin not only in the treatment and control of venous disease, but also in the maintenance of a good quality of life in most patients with CVI (14).

SAFETY AND TOLERABILITY OF OXERUTIN TREATMENT

In all studies conducted to date, oxerutin use has never been associated with important issues concerning its safety, but there is evidence of a good tolerability even after administration for longer periods.

This is emphasized by the recently published results of an interesting study carried out to specifically evaluate the long term safety and tolerability of oxerutin. This study was conducted on 388 patients with CVI (diabetic and non-diabetic) that were included in a large independent clinical registry for a period of 5 years (15). The variations in blood parameters, liver and kidney function tests, microalbuminuria (in patients with diabetes) and cholesterol levels were estimated in order to assess the effects of treatment.

According to investigators, no significant adverse variations were found in blood parameters (hematologic and coagulation) both at 2 years and at 5 years. In patients treated with oxerutin (500-mg tablets or 1 g sachets twice daily), there were reductions in

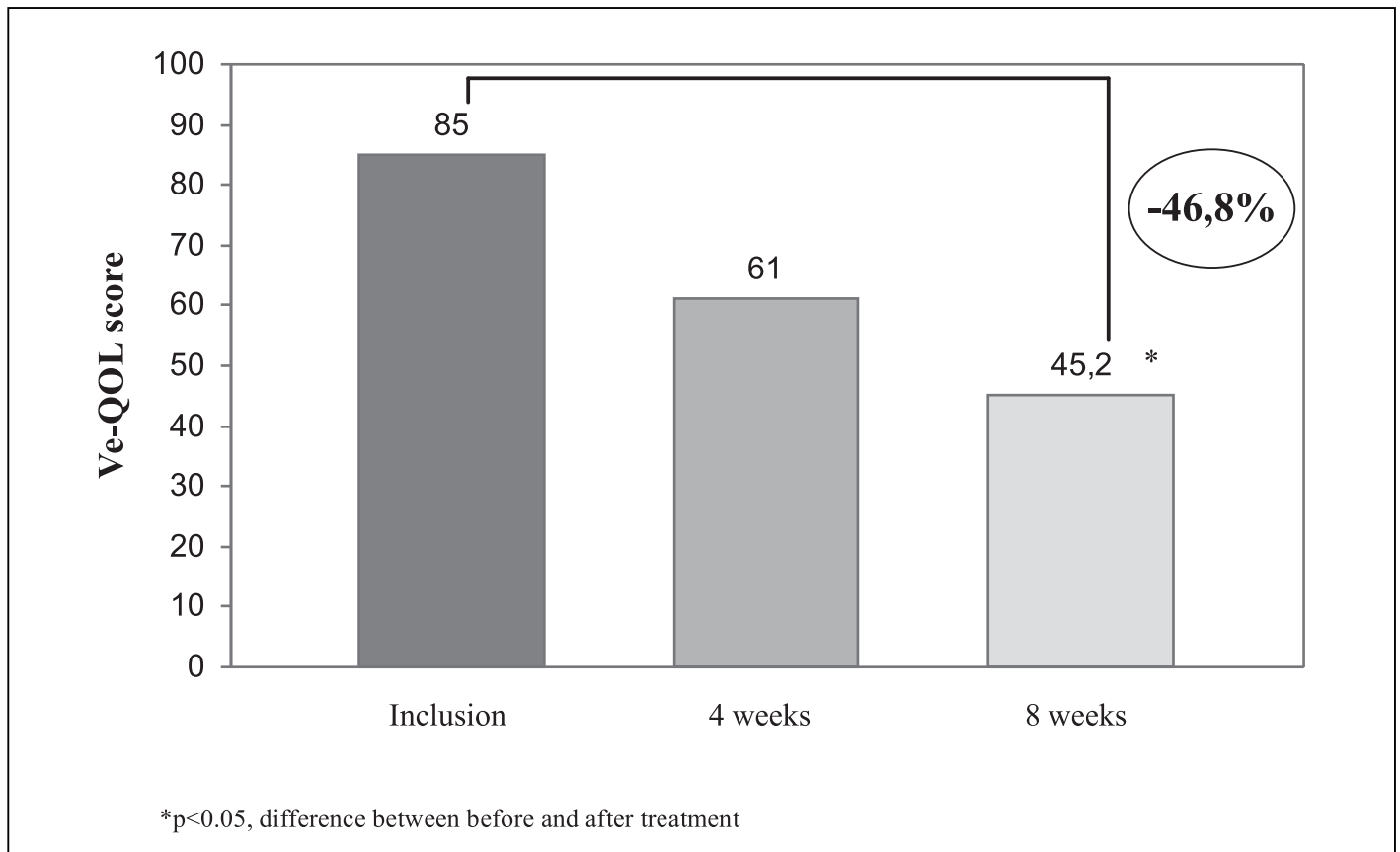


Fig. 3 - Mean changes in Ve-QOL score in patients treated with oxerutin for 8 weeks. Taken from (14).

microalbuminuria and total cholesterol levels, and an increase in HDL cholesterol, particularly in diabetic patients, in contrast to untreated groups where changes in these parameters were minimal and not significant. Therefore, these findings not only have confirmed the safety of long-term treatment with oxerutin, but have also demonstrated positive effects on parameters such as cholesterol levels and microalbuminuria (in patients with diabetes). As the latter parameter is an important risk factor for the development of renal failure, stroke, and cardiovascular disease, we can hypothesize new research perspectives on the metabolic value of oxerutin and rutinoids (15).

CONCLUSIONS

Oxerutin has been used for many years primarily for the treatment of edema, CVI and diabetic microangiopathy, largely because of the positive effects associated with its antioxidant properties and inhibitory effects on inflammation, capillary permeability, and development of atherosclerosis (16).

The action of oxerutin on the microcirculatory capillary and their gel-matrix, with inhibition of increased filtration rate during hypoxic conditions, which is reflected biochemically in the limitation of endothelial damage and in the down-regulation of local pro-inflammatory mediators (leukotrienes), is an essential step to provide a significant improvement in signs and symptoms for patients with CVI (3).

In addition, the characteristics of flavonoids and oxerutin suggest new potential clinically relevant applications for these compounds, including the contrasting action against poor diet (excessive intake of salt, fat or calories in the diet), the protective effects against tumor development and spreading, and against the development of early atherosclerosis, the endothelial protection and the reduction in the adverse effects of radiochemotherapy (16).

Studies in this area have confirmed the efficacy of oxerutin and have demonstrated the safety, versatility and ease of use in both systemic and local administration, thus confirming the clinically relevant benefits in the treatment of venous insufficiency and other important diseases as well.

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MORBID OBESITY AND LYMPHEDEMA: A SYSTEM OF COMBINED TREATMENT

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SUMMARY

Purpose: Morbid obesity associated with lymphedema represents a cause of highly invalidating and life-threatening condition. The purpose of this preliminary report is to propose a system of treatment, assessing the efficacy of a combined approach of both diseases.

Methods: A first series of 10 patients affected by morbid obesity (BMI>40) and lower limb lymphedema (III to V stage) underwent a protocol of global simultaneous treatment of both diseases by Complete Decongestive Therapy (CDT) and Biliopancreatic Diversion (BPD). Patients had been under observation for six-twelve months. Those patients who were not significantly responsive to this kind of combined approach without any significant regression of previous lymphedema staging, unless the significant decrease of body weight, had lymphangioscintigraphy performed in order to evaluate a right indication to LVA.

Results: Weight reduction after BPD was considerable. Six patients showed a significant reduction of lymphedema after the combined approach CDT and BPD procedures, with a high level of patient's satisfaction. Two patients underwent massive localized lipo-lymphedema resective procedures and two patients underwent LVA. Clinical and lymphoscintigraphic post-operative follow-up showed a marked edema and volumetric reduction.

Conclusions: Considering the high incidence of morbid obesity and its not-unfrequent association with lymphedema, the method proposed of a combined approach can represent an effective therapeutic solution of both diseases with a satisfactory metabolic and functional recovery.

INTRODUCTION

Morbid obesity combined with lymphedema, according to Földi M. and Földi E. thesis⁽¹⁾, is more than the sum of the two diseases because it causes the diaphragm to be above its normal position, impairing its movement. As a consequence, a fundamental mechanism that supports lymph flow is significantly decreased. In addition, the other well known common complications of obesity must be taken into consideration (Fig. 1, Fig. 2).

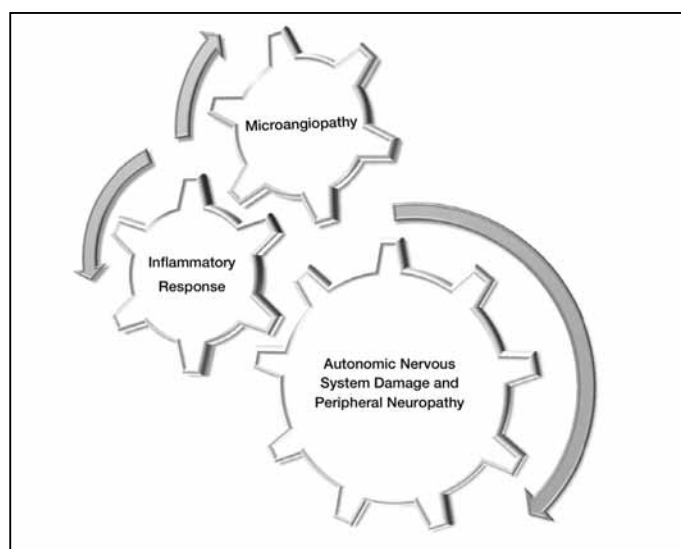


Fig. 1

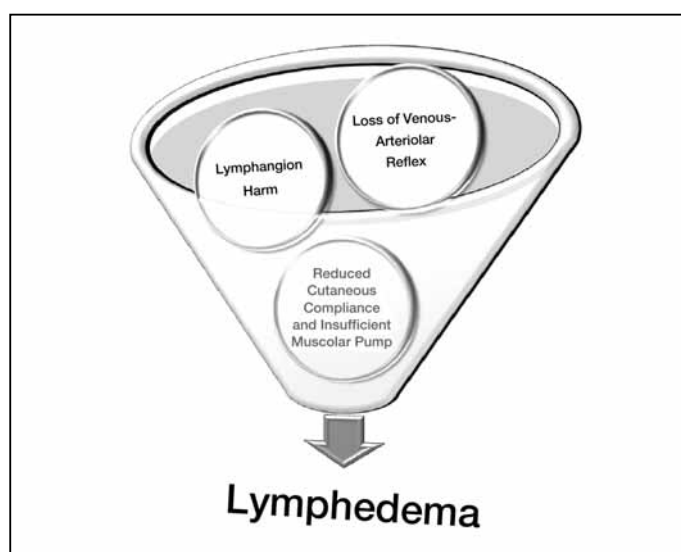


Fig. 2

That's why morbid obesity associated with lymphedema represents a cause of highly invalidating and life-threatening condition.

The purpose of this preliminary report is to propose a system of treatment, assessing the efficacy of a combined approach of both diseases.

METHODS

A first series of 10 patients affected by morbid obesity (BMI>40) and lower limb lymphedema (III to V stage) had been enrolled in this preliminary study (Fig. 3). Patients underwent a protocol of global simultaneous treatment of both diseases by Complete Decongestive Therapy (CDT) according to Földi's method and assessing Bariatric Surgery. All patients were treated with Biliopancreatic Diversion (BPD) according to Scopinaro's procedure⁽²⁾. Patients had been under observation for six-twelve months both on the bariatric point of view and on the CDT method (outpatient phase). Patients were evaluated during this period of follow-up at 1-3-6 and 12 months. After 12 months those patients who were not significantly responsive to this kind of combined approach without any important regression of previous lymphedema staging, notwithstanding the relevant decrease of body weight, had lymphangiostigraphy performed in order to evaluate a right indication to lymphatic-venous microsurgical anastomoses⁽³⁻⁴⁾ and/or massive localized lymphedema resective procedures.

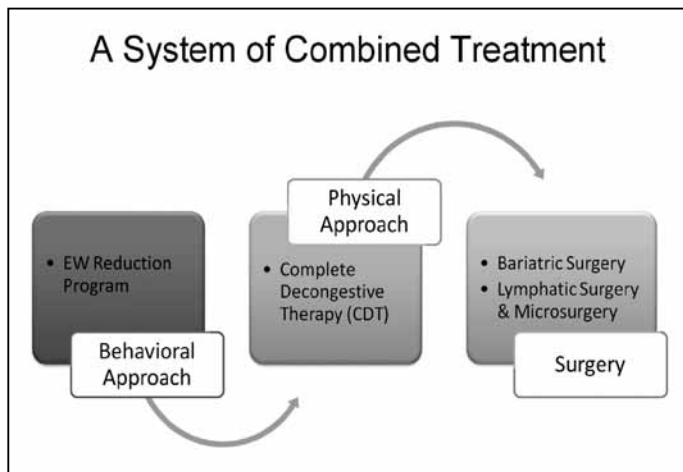


Fig. 3

RESULTS

Weight reduction after BPD, expressed as percentage loss of the initial excess weight (IEW%L), was considerable (>70%). Six patients showed a significant reduction (>50% in comparison to previous volumetry) of lower limbs affected by lymphstasis after the combined approach of the bariatric surgery and CDT procedures, with a high level of patient's satisfaction (Fig. 4). Two patients underwent massive localized lipo-lymphedema resective procedures, with a highly satisfactory result up to 12 months after surgery, both on the functional and on the

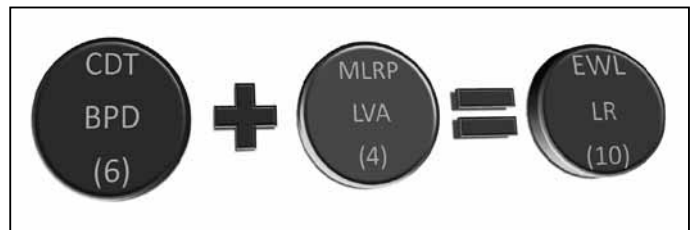


Fig. 4

psycho-cosmetic point of view. Other two patients, on the guide of lymphangiostigraphy showing a relevant impairment of *lymph transport capacity index* of lower limbs, underwent Derivative Lymphatic-Venous Bypass microsurgical procedure (LVA), performing a simultaneous operation at both groin sites (Fig. 5, 6, 7, 8, 9). Clinical and lymphoscintigraphic post-operative follow-up (evaluated at 3-5 years after surgery) showed a long-lasting improvement, with a marked edema and volumetric reduction maintained by a proper lifestyle, remedial exercise, elastic stockings and periodical CDT procedures^(3, 4).

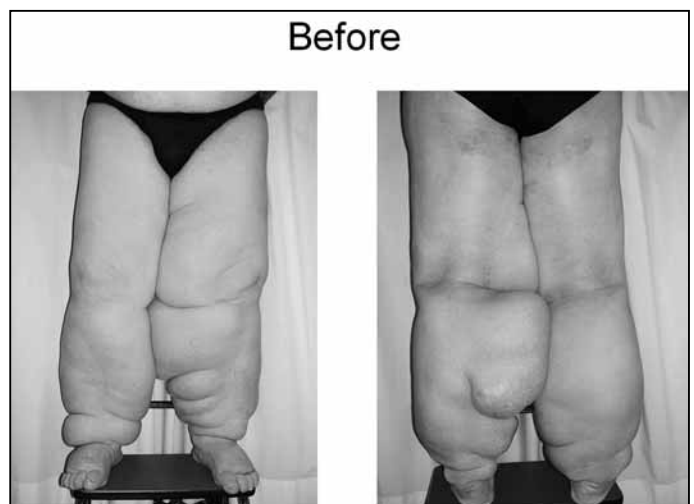


Fig. 5

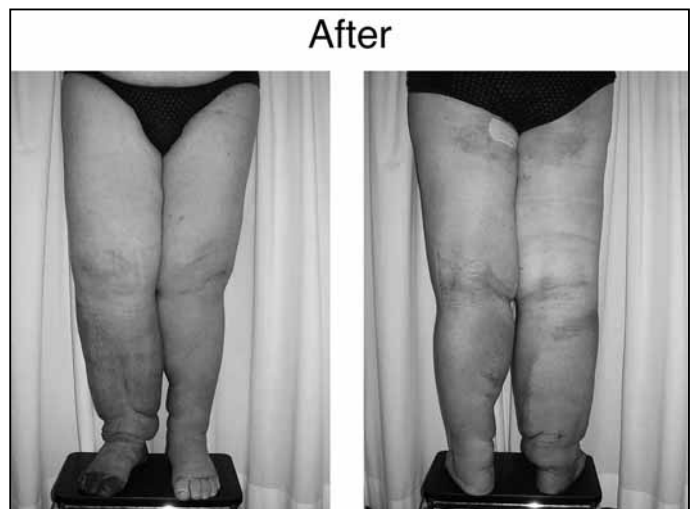


Fig. 6



Fig. 7

Figs. 5-7: Morbid obesity and lymphedema: an example of successful outcome of the combined therapeutical approach.



Fig. 8



Fig. 9

Figs. 8-9: Another case of lymphedema in morbid obesity: the combined treatment allowed to obtain successful results.

CONCLUSION

Considering the high incidence of morbid obesity and the not-unfrequent association with lower limb lymphedema and/or massive localized lipo-lymphedema, the method proposed of a combined approach can represent an effective and long-lasting therapeutic solution of both diseases with a satisfactory metabolic and functional recovery.

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A PILOT RANDOMISED CONTROL TRIAL TO COMPARE A NEW INTERMITTENT PNEUMATIC COMPRESSION DEVICE AND 12-CHAMBER GARMENT WITH CURRENT BEST PRACTICE IN THE MANAGEMENT OF LIMB LYMPHOEDEMA

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This work has been accepted as an oral presentation at the ISL Congress in Sydney, Australia 2009 and will be submitted for an oral presentation at the British Lymphology Society in Sheffield in October 2009.

ABSTRACT

Background: Intermittent Pneumatic Compression (IPC) is used in combination with Medical Lymphatic drainage (MLD) during the intensive phase of Decongestive Lymphoedema therapy (DLT). However the introduction of the LymphAssist™ cycle on the Flowtron® Hydroven 12 could reduce the need for this combined treatment and prove cost effective.

Aims and Objectives: The main aim of this study was to determine if the use of a new pneumatic compression device, the Flowtron® Hydroven 12 used on the LymphAssist™ mode (which mimics medical lymphatic drainage), used in combination with multi layer lymphoedema bandaging was as effective as standard best practice of lymphoedema management in the form of Decongestive Lymphatic Therapy (DLT). Specific objectives were pre and post treatment limb volumes measurement, to determine changes in skin texture and determine a power calculation for further studies.

Design and Methods: The research design was a pilot randomised control trial using mainly quantitative data. The study recruited a random sample of 12 patients who require DLT. Participants' limb volume was measured pre treatment, at day five and ten of treatment and one month later. Other data was collected looking specifically at skin changes and ease of use of therapy. The study included participants regardless of cause of oedema and both upper and lower limb oedema.

Results: The study demonstrated a reduction of limb volume and skin thickening in both patients groups. It demonstrated that limb volumes did not return to the pre treatment measurements at one month follow up in either group. There was a reduction of thickening of the tissues in both groups indicating a reduction of macromolecules.

Additionally the Flowtron® Hydroven 12 on the LymphAssist™ mode was easy to use and pleasant for the patient.

Conclusion: The findings support the inclusion of the 'LymphAssist' to be used as part of standard lymphoedema management. As a feasibility study, a power calculation was determined and improvements in the randomisation and analysing upper and lower limb separately are recommended for further studies. In conclusion the Null hypothesis that patients treated with Flowtron® Hydroven 12 using the LymphAssist™ mode will experience no greater limb volume reduction than patients treated with standard best practice lymphoedema treatment using MLD and multilayer bandaging was confirmed.

INTRODUCTION

"Lymphoedema is a progressive chronic condition that affects a significant number of people and can have deleterious effects on patients' physical and psychosocial health"⁽¹⁾. Lymphoedema is a chronic swelling usually of a limb caused due to lymphatic failure either from a congenital abnormality or due to damage to the lymphatic system⁽²⁾.

Best practice in lymphoedema treatment has been the main aim of many professional and patient oriented organisations, striving to provide gold standard equitable care to patients with lymphoedema^(3,4,1). However, the defined best practice of these organisations, is largely based on consensus and anecdotal evidence. Reasons for this are mainly due to the lack of available randomised controlled trials (RCTs) in this specialist field of work and the absence of NICE guidelines for the care of the patient with lymphoedema. The Lymphoedema Framework produced its best practice document for the management of lymphoedema in 2006

but the use of pneumatic compression, the basis of this study, only features minimally. This study compared 'best' practice of lymphoedema treatment with a new intermittent pneumatic compression therapy device to assess its ability to provide best practice treatment.

One of the mainstay treatments for lymphoedema therapy in Europe is Intermittent Pneumatic Compression⁽⁴⁾. During the 1950s, treatment with IPC was used as common practice in the United Kingdom (UK) being virtually the only treatment available for lymphoedema. The introduction of evidence based care and other treatment strategies, which are now nationally well established, has seen the decline in the use of IPC over the last decade. Therapists have been hesitant to use IPC although risks considered related to its use are preventable and exist from outdated treatment programmes and concerns that IPC induces genital oedema⁽⁵⁾.

The International Society of Lymphology (2003) and the Lymphoedema Framework (2006) highlight IPC to be an essential part of lymphoedema management yet its use is rarely discussed in the UK as part of combined treatment and many therapists do not have access to machines. IPC is recommended to be used as part of DLT in combination with multi layer bandaging, MLD and exercise to provide part of a holistic treatment regime.

In 1998, Boris et al.⁽⁵⁾, linked its use with inducing genital oedema and Eliska and Eliskova (1995) published research to show that 'high pressure massage could damage the fragile lymphatics'⁽⁶⁾. This saw the declined in use of IPC in the UK with therapists preferring to use the more gentle technique of MLD in combination with multilayer bandaging. Other controversy surrounding the use of IPC is research highlighting that by removing the water component of the interstitial fluid via reabsorption into the veins and not the lymphatics the tissues become more fibrosed through a build up of macromolecules, concentrating the lymphoedema⁽⁷⁾. Belgrado et al. (2007) in their review of IPC literature state the function of the "mechanical action of IPC is limited in returning macromolecules back to the circulatory system via the lymphatics or the veins"⁽⁸⁾. Leduc therefore recommends that IPC should only ever be used in conjunction with MLD (Leduc method) which is designed to remove protein. However, Miranda et al. (2001) demonstrated through lymphoscintigraphy that IPC enhanced the lymphatic transport to the proximal parts of the limb but did not transport macromolecules and Brennan and Miller (1998) stated that retained fluid was brought to the functioning lymphatics^(9,10). The effectiveness of IPC is also somewhat in debate where Dini et al. (1998) report that its effectiveness was statistically insignificant at a follow up appointment after a 6 week trial, but a reduction was statistically significant compared to the control group at the end of the treatment⁽¹¹⁾. As the subjects did not wear compression hosiery it is easy to assume that the IPC reduced the oedema only to increase later when therapy stopped and hosiery was absent. It is essential for compression hosiery to be worn to maintain results of treatment as refill of the tissues is inevitable. The device used in this study was also unknown and will not have had the unique LymphAssist™ mode designed in 2005, used for the research in this study. Roper et al. (1999) also report a reduction of arm

volumes in stroke patients following treatment with IPC but reported that treatment was "not effective" at evaluation but again this was not maintained due to not providing compression garments following treatment and maintaining the reduction⁽¹²⁾. Richmond, O'Donnell and Zelikovski (1985) carried out the only available literature on lower limb swelling, termed "A controlled trial"⁽¹³⁾. They treated twenty-five lymphoedema patients with an undisclosed sequential pneumatic compression pump for 24 hours obtaining a maximum reduction of 47% at the mid calf region concluding that the pump "reduced lymphoedematous limb rapidly and safely".

Several studies have compared IPC with MLD but all use a treatment group of lymphoedema following breast cancer treatment and are conducted with patient numbers of less than thirty participants^(14,15,16). Johansson et al. (1998) and Skall et al. (2003) did not find any significant difference between either of the groups receiving IPC or MLD but Johansson et al. (1998) report that MLD or IPC used with compression garments results in a "notable reduction of arm lymphoedema". Szuba et al. (2002) reported that IPC enhances the other treatments used in a DLT treatment regime and shows a significant difference in reduction of limb volume at the end of treatment for patients receiving IPC compared to those in the control group⁽¹⁶⁾. This study organised two groups of patients, those who had received previous DLT and used IPC as a self administered treatment at home and those who received IPC as an adjunctive to standard DLT. Both groups of patients saw a reduction in limb volume but no further reduction once IPC therapy had been stopped at 1 month. Johansson et al. (1998) use IPC as a stand alone treatment by providing the patients with either 45 minutes of Vodder MLD or 2 hours of IPC at a pressure level of 40-60mmHg. There is no literature available relating the length of time IPC should be administered to compare it to MLD but a comparison of 45 minutes of MLD for 2 hours of IPC seems inequitable in this study. The IPC used in this study was a 9 chamber "lymphapress" whilst Szuba et al. (2002) used a 4 chamber pump and Newman (1988) a one chamber pump⁽¹⁷⁾. There is evidence to suggest that multiple chambers maybe more effective than single chamber pumps⁽¹⁸⁾. These studies were used to identify the effectiveness of IPC but maybe introduce us to a stand alone treatment for lymphoedema with the exclusion of compression garments. Certainly the authors' lymphoedema service uses the Flowtron hydroven 12 on the LymphAssist™ mode for preventative management and long term maintenance instead of MLD and has not seen an increase in concentration of tissue.

Controversially, the one paper linking the development of genital oedema to compression pumps indicates pumps were used at high pressure for long periods of time⁽⁵⁾. As a retrospective study, the patients had limited supervision and monitoring, which would not have allowed for the early detection of genital oedema. The current study specifically observes for the presence or development of genital oedema in the patients treated with lower limb oedema. There are no other reports of genital oedema induced by IPC although several case reports have linked genital oedema in the labia related to trauma experienced by competitive female cyclists from intensive training⁽¹⁹⁾. MLD was found to assist in resolving this problem.

A negative aspect of IPC is its contraindication in patients with cardiac problems. Olivier Leduc and colleagues (1990) showed that the use of the IPC induced pressure in the right atrium in patients with heart failure⁽²⁰⁾. However, this was a controlled experiment carried out within the cardiac unit. Its effects ceased immediately the pump was stopped but gives a strong indication that pneumatic compression must not be used on patients with cardiac failure. The LymphAssist is not able to exert pressures of more than 40mmhg and therefore should not have the same effect.

MATERIALS AND METHODS

The study is the first to use the Flowtron® Hydroven 12 on the LymphAssist™ mode. The study was a pilot randomised feasibility study carried out on patients in whom IPC was utilised as part of an intensive treatment programme instead of and in comparison to MLD with both groups having multi-layer bandaging. The Flowtron® Hydroven 12 was utilised on the unique LymphAssist™ mode that aims to mimic MLD. The Flowtron® hydroven 12, was designed to address many of the above contraindicated issues. The Flowtron® Hydroven 12 uses a garment consisting off twelve overlapping inflatable pockets which inflate and deflate individually. The inflation and deflation rates and chamber pressures can be altered to suit each individual patient and situation⁽²¹⁾. The unique pump cycle can not apply pressures greater than 40mmhg, commences proximally to distal, always completes a full cycle and is designed specifically to provide 5 mini inflations in each chamber to assist “inciting”⁽²²⁾. The study also utilised a client group of both primary and secondary lymphoedema and upper and lower limb, unlike any of the previous comparisons^(14,15,16,17). In addition the IPC will be used as part of a DLT treatment regime.

The main outcome measures were deemed to be measurement of limb size (limb volume reduction), to gather data to make a power calculation and to measure skin change (thickening). Secondary outcomes were pitting of the tissues and length of time with lymphoedema and patient response to treatment.

Scheduled treatment

Patients were randomly selected to either the control (standard treatment) or treatment group (LymphAssist). All patients attended for daily for two weeks for MLD (Leduc method) and MLLB or LymphAssist and MLLB. MLD was carried out for approximately 45minutes and LymphAssist 2 cycles at 30-40mmhg was provided (1 cycle is approximately 19 minutes). Data collection took place on day 1,5,10 and 1 month. Following 2 weeks intensive treatment, maintenance was achieved with reducing session of MLD or LymphAssist, 3 x week for 1 week, twice week for 1 week and weekly for 4 weeks. The patients would wear compression garments for 24 hours a day for 6 weeks removing only for hygiene and skincare purposes. This is normal practice and treatment regime within the study treatment centre.

Patient selection consisted of all patients requiring DLT who were recruited between November 2007 and September 2008.

Inclusion criteria

- Aged 18 years or more.
- Lymphoedema of a limb (arm or leg).
- Able to understand the purpose of the study and is willing to give written consent.
- Able to attend for treatment 5 times per week (daily) for 2 weeks (10 days) and a follow up appointment.

Exclusion criteria

- Significant arterial disease (ankle brachial pressure index – [ABPI] <0.8) or those who had clinical signs of arterial disease if Doppler investigation was unable to be performed.
- Cellulitis of tissues of the affected limb.
- Acute or within 6 weeks of a deep vein thrombosis (DVT).
- Pitting oedema associated with cardiac, renal or liver failure.
- Oedema in an adjacent area of the trunk.
- Active cancer at the root of the limb or in the adjacent quadrant.
- Wound or other skin condition that would be aggravated by the garment (i.e. allergies).
- Lymphorrhoea.
- Those who could not commit to two weeks of standard intensive lymphoedema therapy⁽¹⁾.

Ethical approval was gained through the local ethics procedure.

Data collation and materials used consisted of:

- Extent of oedema,
- Limb Volume - lower limb by perometry,
- Limb volume - upper limb by circumferential measurements,
- Skin condition,
- Skin thickening,
- Pitting test,
- Photographic comparison,
- General improvement,
- Flowtron® Hydroven 12 pneumatic compression- pump used to administer pneumatic compression,
- MLD (Leduc Method)- method of lymphatic drainage used to administer lymphatic drainage,
- Presence of Genital Oedema.

Data Analysis

Data analysis was undertaken by the statistical software package SPSS for windows version 16. For the purpose of the pilot study and due to the extensive data collection, only the data that was deemed the most relevant to the trial and researcher was analysed. Subsequent data will be analysed at a later date. Subjects were identified using their unique identifying number to determine demographic data consisting of gender, age, cause, age at onset and length of time with condition in addition to site, and pre, inter and post limb volumes and pre, inter and post thickening and pitting levels. The power calculation for this study was calculated using power calculation software package and SPSS.

As there was not a normal distribution curve non parametric tests were required to assist analysis. The collective data was analysed using inferential and descriptive statistics. The pilot study consisted of 12 data collection packs of which analysis was carried out on 11 due to one subject being excluded from the trial. On completion 69 variables were available.

RESULTS

The sample size was too small to ensure any normal distribution curve of the sample and therefore non parametric tests were necessary for statistical analysis.

12 patients were recruited to the study with one set of data being excluded from analysis due to the patient being unable to comply with treatment and therefore the results may have been skewed. The demographic data is shown in table 1-5. The all subjects were female, with a mean age of 54.4 in the treatment group and 62.8 in the control group (table 2). The site of the oedema in the treatment group were 2 upper limb, 1 lower limb and 2 bilateral, and in the control group were 3 upper limb, 1 lower limb, 2 bilateral oedema (table 3). The average length of time with oedema was 14.45 years and ranged from 1-50 years. However the length of time is not normally distributed with 6 subjects having oedema for less than 4 years (table 4). Table 5 shows the level of severity of the condition with the treatment group displaying slightly more severe lymphoedema at commencement of treatment. Table 6 demonstrates a major outcome measure showing 100% improvement of limb volume reduction in both groups at day 10.

Table 1 - Treatment groups

Number of subjects	11 (gender female)
Treatment group	5 (gender female)
Control group	6 (gender female)

Table 2 - Age range

Mean age	59 (range 36-79)
Mean age (treatment group)	54.4 (range 36-71)
Mean age (control group)	62.8 (range 38-79)

Table 3 - Site of oedema

Site of oedema	Treatment group	Control group
Upper limb	2	3
Lower limb	1	1
Bilateral	2	2
Total	5	6

Table 4 - Length of time with oedema

Years	1	2	4	15	18	22	43	50	Total
Number	3	2	1	1	1	1	1	1	11

Table 5 - Level of severity

Level of severity	Treatment group	Control group	Total
Mild	0	1	1
Moderate	3	4	7
Severe	2	1	3
Mean	2.4	2.0	2.2

Table 6 - Improvement at day 10

Improvement in limb volume	11
Increase in limb volume	0

The histogram (chart 1) of limb volume does not show a normal distribution as was consistent with the other data analysis. In this instance there were more subjects with a smaller limb volume than larger. This is present due to arms having a smaller limb volume than legs and a total volume being used for bilateral oedema and all volumes being analysed together. Table 7 shows the mean limb volume measurements for both groups at baseline, day 5, 10 and at 1 month review. Both groups show a reduction at day 10 but an increase at one month. When comparing baseline to one month the volumes have reduced and did not returned to pre treatment levels. Using the nearest non-parametric equivalent of a 2 way Analysis of Variance (ANOVA) test by subtracting the baseline score from each of the outcome measurements and comparing the groups, the results show that there was no significant difference between the treatment and control group. This also indicates that wearing of compression garments 24/7 following DLT maintains limb volume. However, some patients did experience problems with garments which is shown in an increase in volume.

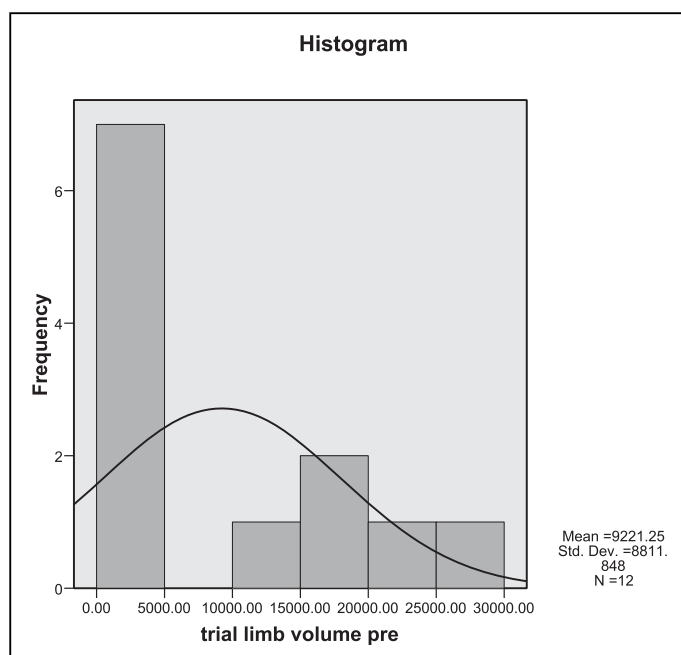


Chart 1

Table 7 - Changes in limb volume baseline to 1 month

Treatment group		Trial limb volume pre	Trial limb volume day 5	Trial limb volume day 10	Trial limb volume 1/12	Limb volume base to day 5	Limb volume base to day 10	Limb volume base to 1 month
Treatment	Mean	12068.2000	11149.6000	10986.8000	11368.2000	918.6000	1081.4000	700.0000
	N	5	5	5	5	5	5	5
	Std. Deviation	10094.38127	9694.11978	9484.91237	9826.46545	1017.71204	1097.48613	904.70382
Control	Mean	10553.6667	9654.0000	9599.6667	10102.0000	899.6667	954.0000	451.6667
	N	6	6	6	6	6	6	6
	Std. Deviation	10328.23351	9367.00251	9405.52888	10319.42312	1150.46767	1224.22678	495.41565
Total	Mean	11242.0909	10333.8182	10230.1818	10677.5455	908.2727	1011.9091	564.5455
	N	11	11	11	11	11	11	11
	Std. Deviation	9732.44070	9059.29318	8985.66508	9607.61518	1037.39135	1111.56758	683.32487

There was a bigger limb volume reduction seen in the treatment group even though they started with a larger pre volume. This could show that the treatment group was maintained better with LymphAssist. However, as the limb volume was larger in the first instance it could be argued that due to the larger capacity the limbs had further to reduce.

The thickening also was worse in the treatment group also so typically with increased volume and thickening you would expect less reduction. Statistically nevertheless, again there is no significant difference.

Table 8 Shows a reduction of tissue thickening was noted in both groups at day 10 with measurements still smaller than pre-treatment levels at 1 month. There was a continued reduction of 1.0 in the control group from post treatment to 1 month and an

increase in the treatment group at 1 month but not to pre treatment levels. This may demonstrate the continued reduction of macromolecules with the control group receiving MLD and could support evidence that IPC does not continue to reduce protein without multi layer bandaging 23. However, there is no statistical significance only that both groups had a reduction in thickening and therefore protein.

Other data supports that the Flowtron Hydroven 12 was beneficial in limb volume reduction, provides a good alternative to MLD and is easy to use (table 9, 10, and 11)

Table 12 and 13 show the patient response to treatment with 100% improvement shown.

Table 8 - Changes in skin thickening from base - 1 month

Treatment condition		Thickening trial limb pre	Trial limb thickening day 5	Thickening trial limb day 10	Trial limb thickening 1/12	Thickening base to day 5	Thickening base to day 10	Thickening base to 1 month
Treatment	Mean	2.4000	1.5000	1.2500	1.4000	1.0000	.5000	.7500
	N	5	4	4	5	5	4	4
	Std. Deviation	1.14018	.57735	.50000	.54772	1.00000	.57735	.95743
Control	Mean	2.0000	1.5000	1.8000	.8333	1.1667	.5000	.4000
	N	6	6	5	6	6	6	5
	Std. Deviation	.63246	.54772	.44721	.40825	.75277	.54772	.54772
Total	Mean	2.1818	1.5000	1.5556	1.0909	1.0909	.5000	.5556
	N	11	10	9	11	11	10	9
	Std. Deviation	.87386	.52705	.52705	.53936	.83121	.52705	.72648

Table 9 - Clinical assessment of limb volume and tissue appearance

	Frequency
Beneficial volume reduction and appearance	9
Beneficial to tissue appearance only	1
Total	10

Table 10 - Comparison with standard treatment

IPC comparison to standard treatment (therapist view)	Number
Reasonable alternative	3
Use in association with	1
Total	4

Table 11 - Ease of use

Is IPC easy to use?	yes	NO	Missing
	4	0	1

Table 12 - Patient ratings of treatment

Treatment condition		N	Mean Rank	Sum of Ranks
Patient assessment of limb size	Treatment	4	5.50	22.00
	Control	6	5.50	33.00
	Total	10		
Patient assessment of pain	Treatment	3	2.67	8.00
	Control	1	2.00	2.00
	Total	4		
Patient activity level	Treatment	3	5.00	15.00
	Control	5	4.20	21.00
	Total	8		
Patient therapy rating	Treatment	4	5.75	23.00
	Control	6	5.33	32.00
	Total	10		
Patient general wellbeing	Treatment	4	3.88	15.50
	Control	5	5.90	29.50
	Total	9		
Patient overall opinion	Treatment	4	5.25	21.00
	Control	5	4.80	24.00
	Total	9		

DISCUSSION

The main limitation of the study was the sample size which was too small to provide statistical significance and was due to recruitment issues. It was perceived that the trial was very inclusive in reality recruitment was difficult.

However the purpose of a feasibility study is to highlight issues to consider for a larger study.

Reasons for poor uptake of the study are listed below.

1. Time commitments from the patient.
2. Reluctance to wear garments 24/7 for 6 weeks.
3. Patients choosing not to undertake DLT.
4. Patients prefer one treatment and not wishing to undertake randomisation.
5. Full treatment schedules could not be offered due to several bank holidays during the trial period.
6. Some patients were deemed by the recruiting therapist to be in compliant and would not tolerate the treatment.
7. Recruitment was delayed due to not all staff being MLD trained.
8. Patients were deemed too old/ frail or not in a social situation

Table 13 - Analysis of patient questionnaire

Treatment condition	Patient assessment of limb size	Patient assessment of pain	Patient activity level	Patient therapy rating	Patient general wellbeing	Patient overall opinion
Mann-Whitney U	12.000	1.000	6.000	11.000	5.500	9.000
Wilcoxon W	33.000	2.000	21.000	32.000	15.500	24.000
Z	.000	-.577	-.775	-.244	-1.207	-.283
Asymp. Sig. (2-tailed)	p=1.000	p=0.564	p=0.439	p=0.807	p=0.227	p=0.777
Exact Sig. [2*(1-tailed Sig.)]	1.000	1.000	.786	.914	.286	.905

- to undergo “standard best practice” treatment and may not comply following treatment.
9. 2 patients were excluded due to learning difficulties.
 10. One patient was excluded due to suspected recurrent disease.
 11. Patients with Lymphorrhoea were excluded from the trial but required urgent treatment and therefore increased waiting for trial patients.

It is also accepted that there are several confounding variables within the study. These include the experience of the therapist carrying out the bandaging treatment as generally the non MLD trained therapists treated the patients in the treatment group whilst the more experienced therapists who were trained in MLD would treat the control group. In addition the experience of therapists ranged from 6 months to 15 years.

ABILITY TO COMPLY

One patient, in the treatment group, had entered into a new relationship following a recent divorce. She was particularly un-compliant in the maintenance phase of treatment and did not wear her garment 24/7 as protocol. Although regarded as an ‘expert patient’ with a very stubborn and difficult to control oedema, she found the maintenance phase particularly problematic psychologically and therefore incurred a rebound of 2000mls at 1 month.

POWER CALCULATION

One of the main outcomes of the study was to ascertain a power calculation for further study. Only 12 participants were recruited when intending the recruit 40. The main outcome measure used for the power calculation was limb volume reduction at 10 days and 1 month with the latter showing long term maintenance of the condition. For the purpose of further studies, the 10 day outcome measure is recommended due to the other non-controllable influencing factors in the subsequent 2 weeks. Power was ascertained using the mean and standard deviation of the outcome measures. A sample size of 22 in each group would provide a 90% confidence level and error of 0.05 with a type 1 error. Interestingly the original sample size selected was 40 participants, 20 in each group, suggesting that without a power calculation prior

to the study, the sample size would have been sufficient to show significance should recruitment issues not have been so problematic.

EFFECTS OF STUDY OUTCOMES AND RECOMMENDATIONS

The results of this study will ensure that the use of Flowtron® hydroven 12 on the LymphAssist™ cycle has a secure place in the future of lymphoedema management. This assists in lymphoedema management by reducing limb volume and reducing thickening to the limb. It is also acceptable to the patient and can reduce the risks involved to therapist from repetitive strain injuries. Genital oedema was not reported in any of the patients in the treatment group (those using the LymphAssist™ mode) and shows that with careful observation, selection and monitoring the inbuilt reduced pressure on the LymphAssist™ mode does not induce genital oedema. In addition the study centre has treated over 100 patients with the Flowtron® Hydroven 12 on the LymphAssist™ mode and has not noted and genital or trunkal oedema from the pump. In addition there is little evidence that the LymphAssist™ mode concentrates the protein content of the lymphoedema which causes skin changes and increased thickening. However it is recommended that the manufacturers carry out lymphoscintigraphy which would provide conclusive evidence of the mechanism of the “LymphAssist™” mode. For further studies it is recommended that analysis of limb volume should be split into upper and lower limb. Generally upper limb oedema is unilateral providing the non-oedematous limb as a control and lower limb oedemas generally have a larger volume. When looking at distribution curves separating the two groups will allow for improves statistical analysis.

CONCLUSION

This study was carried out as a feasibility study to determine the need and changes required to progress to a full Randomised Controlled Trial. The power calculation has identified recruitment number. In conclusion the Null hypothesis that patients treated with Flowtron® Hydroven 12 using the LymphAssist™ mode will experience no greater limb volume reduction than patients treated with standard best practice lymphoedema treatment using MLD and multilayer bandaging was upheld. The LymphAssist™ mode used as part of a treatment regime is as effective as standard best

practice using MLD. In addition both standard best practice and LymphAssist™ reduce limb volume and tissue thickening, do not cause genital oedema and patients tolerate treatment with gains in mobility and comfort.

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LYMPHOEDEMA POST-MASTECTOMY: PRIMARY PREVENTION

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ABSTRACT

In our laboratory of lymph-angiology, over a period of 7 years, we have followed 304 patients affected by secondary post-surgical upper limb lymph-oedema and we have decided to focus our attention on stage Ia, 22% of patients, which includes patients at risk of developing lymph stasis in the homolateral arm, without clinical evidence of oedema. (Photo 1).

MATERIALS AND METHODS

Patient evaluation, inside the rehabilitative team, with the inclusion of other different disciplines, leads to a clinical report where anamnesis and clinical examination were included. When we talk about primary prevention, lymph-scintigraphic exam is the most important because it permits the study of the anatomic-functional lymph flow system in the homolateral arm, but, above all, because it allows us to identify patients at risk of oedema onset: those who present slower radiotracer flow (presence of lymph-node stops along the arm and/or initial dermal back flow) which might not otherwise be identified. (Photo 2). This investigation was performed by subcutaneous radiotracer injection into the interdigital folds.

22% of the patients refused to undergo the exam, while in those who underwent the exam, lymph-scintigraphy highlighted a slower radiotracer flow in 73%, sign of a propensity to develop lymph-oedema.

In the case of no lymph-scintigraphy or no evidence of slower radiotracer flow, only follow-up was required: one yearly check, as well as the participation in the informative group, about which I will give further information later, while in slower radiotracer flow, patients were included in early treatment after the opening of a rehabilitative project.

The early treatment consisted of MLD and the activation of alternative pathways. (Photo 3). Furthermore, during the rehabilitative treatment, the physiotherapist taught able and motivated patients some simple self-drainage manoeuvres which were also included in an illustrated brochure given to them.

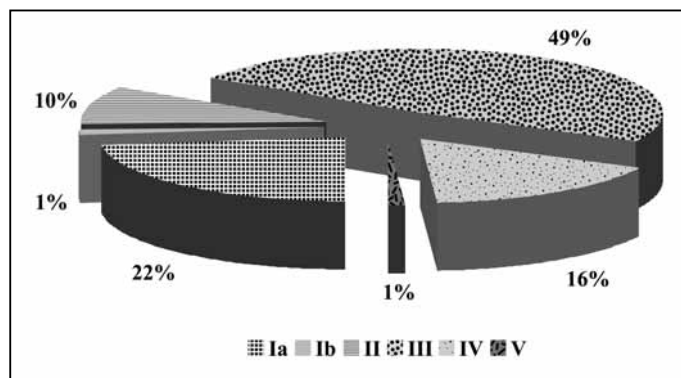


Photo 1

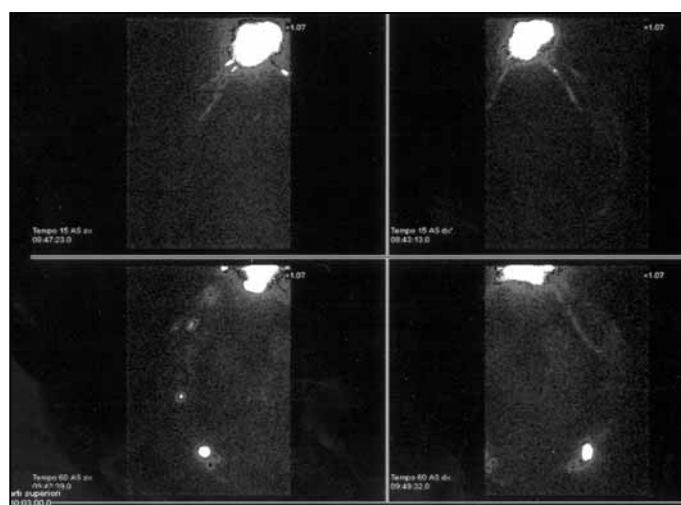


Photo 2



Photo 3

Furthermore, lymph-scintigraphy with homolateral slower radiotracer flow also highlighted contralateral slower radiotracer flow in 29% of the cases: in these cases modified MLD and self-drainage was carried out without utilization of contralateral axilla. At the end of the rehabilitative treatment natural coumarine 6 mg/die for 90 days was prescribed during summertime and a standard I class compression sleeve was recommended during normal everyday activities.

It is therefore essential, that the patient undergoing mastectomy, should be informed, clearly and simply, about lymph-oedema and must cooperate actively and critically towards the primary prevention. So we organize informative groups composed of an angiologist, a physiotherapist, a psychologist and 15 patients with coincident arms or affected by lymph-oedema together. The end-point of the informative group is the information on primary prevention, the information on the pathology, the acceptance of hygienic-behavioural rules and active listening to women's problems.

The physiotherapist explains, simply and clearly, the anatomy and physiology of the lymphatic system, and highlights the importance of the hygienic-behavioural rules to be carried out routinely every day. Patients have to interpret these rules not as prohibitions that could lead to anxious or depressing feelings, but as a fundamental behavioural strategy. A brochure, which contains the above-mentioned hygienic-behavioural rules, is given to the patients. The angiologist gives information on the primary prevention, talks about the pathology and gives information on skin care to be carried out normally and immediately after an injury. The psychologist listens actively to the women's problems and becomes available for individual sittings.

RESULTS

No lymph-oedema onset in patients with no homolateral slower radiotracer flow was observed, while 11% of the patients with homolateral slower radiotracer flow experienced lymph-oedema onset always secondary to accidental or an avoidable event in previously informed patients (strain, burn, pressotherapy). (Photo 4).

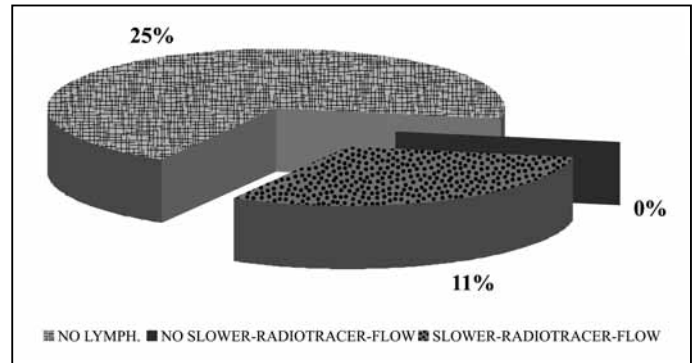


Photo 4

75% of the patients who did not undergo lymph-scintigraphy did not effectuate the recommended yearly check-up, while 25% of the remaining patients had oedema onset, with no apparent cause or after an accident.

CONCLUSION

Even if these results encourage us to continue in this direction, as a rehabilitative team, we must commit ourselves to undertake further dedication in order to attain the complete compliance of the patients. Furthermore, it is still necessary in our reality to continue to fight against the behaviour of the medical world. The information about behavioural rules given to the patients in the post-surgical period is considered enough: so nobody talks about the informative groups which include patients arrived at our centre for examination, spontaneously following request to their general medical doctors; while lymph-scintigraphy exam and the possible, subsequent early treatment is considered a kind of stressing "medicalization".

Obviously this attitude leads to interference in the achievement of early primary prevention.

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NOTICE 1

ESL Award – Papamiltiades and Caplan

Starting from the 2008 the European Society of Lymphology began again to confer the Papamiltiades and Caplan award to one of best paper presented to the national or international Congresses of lymphology by the ESL members during the year.

The paper awarded in 2008 was *The surgical management of chronic penoscrotal lymphedema* by Wald Martin, presented in the national Congress of the Czech Society of Lymphology and published on the European Journal of Lymphology and related problems. The price consisted in the iscription to the 22° World Congress of the International Society of Lymphology in Sydney-2009.

Dott. SANDRO MICHELINI

President of the European Society of Lymphology

NOTICE 2

Highlights of the 34th ESL Scientific Meeting in Napoli and nominees for the PB Lymphological Awards 2008

The overall quality of the meeting was good.

We had a good surgical session with the main following points being achieved and/or questions being raised:

- In the upper limb edemas, the Lympho-Venous anastomosis are merely to be proposed to the stages 2 and 3 (Campisi *et al.*).
- Brorson and colleagues presented their results with liposuction in lower limb edemas and confirmed the strict indications of such interventions.
- Their results seem to outline a shift in the overall cellular mass of the edematous limbs from being “liquid” towards one accumulation of fats in the pre-existing adipocytes and/or in other cells. The question remains to be solved and the mechanisms implied to be identified.

- On the another hand, the question of the importance of the deep lymphatic system in such situations was raised as well as the possibility in such case to associate to such liposuctions LVA or lymph vessel grafting (as proposed by Baumeister and colleagues to bridge the gap).

Belgrado and colleagues presented us interesting results about the variations of pressure and of temperature in patients or subjects wearing multi-layered bandagings. They demonstrated for instance that they resulted in one 4°Celsius increase of the skin temperature, a factor which might be implied in the therapeutic response to such bandagings. They also show us fascinating pictures of the skin temperatures obtained using infra-red technique analysis in patients with limbedemas. The work is in progress but this represents surely another way to study the edematous limbs.

In the same spirit, Leduc and colleagues presented the absence of influence of MLD on cardiac parameters as well as one

NEWS

interesting morphological approach for the formation of the axillary web syndrome.

With regard to more basic researchs, Lievens and colleagues and Bernas and colleagues also presented us two different animal models to study the effects of external irradiation on the lymphatic system regeneration after surgical interventions. The first group used mice and a single vessel lymphatic cutting (the one linking the inguinal node to the axillary one in the animal). They confirmed their presentation in Prague that the (not severed) lymphatic vessels are radio-resistant and they showed that the lymphatic function was restored by lymphatic regeneration through the scar and/or by the development of lymphatico-lymphatic collateralisation pathways. The most surprising fact among their results was that the transport of radiolabeled colloids from the injected lower limb in the axillary nodes was increased when compared to normals, suggesting that there is a (temporary?) overall stimulation of the lymphatic function. On the other hand, Bernas and colleagues used rats as models and their surgical interventions at the root of the limbs was larger than the one performed by Lievens and colleagues. They also demonstrated the effect of Amifostine on the wound regeneration. The two models are interesting but different. For their part, Eliska and Eliskova studied the radial pressure in lymphatic vessels under manual lymphatic drainage.

With regard to clinical situations, Maccio and colleagues stressed the importance of teaching the physicians of the Emergency Units about the lymphangiological

emergencies. On the other hand, Loskotova and Loskotova as well as Michelini and colleagues reminded us the muscular and articular involvements in lymphedemas.

Forner-Cordero and colleagues presented a very good multicenter work comparing in three randomised groups of patients the effects of three physiotherapeutic "regimens". Although there may be a bias in their analysis, the most amusing conclusion was that Manual Lymphatic drainage adds nothing to pressotherapy and Multi Layered Bandagings. Unfortunately, because they were already nominated one year ago for the PB Lymphological Award, they could not be taken into account for the present meeting.

Finally, the three best and most interesting presentations were the following (and their authors are nominated for the PB Lymphological Awards 2008):

- Using immuno histological methods, Okada from Japan showed the different evolution of the veins and lymphatics with the mass of (in the epicardium of) hypertrophic hearts,
- Michelini and colleagues reported their first results with a vaccine in patients to prevent phlogistic complications in lymphedematous patients,
- Cestari and colleagues presented their results in the primary prevention of post-mastectomy lymphedema using one algorithm defining patients at risk.

Prof. Pierre BOURGEOIS, MD, PhD

*Past President of the European Society of Lymphology
Founder and past Editor in Chief of the European Journal
of Lymphology and Related Problems*

ROLE OF AGE-RELATED CHANGES OF LYMPHATIC DRAINAGE RATE IN THE DEVELOPMENT OF EXOGENOUS INTOXICATION AND POSSIBILITIES OF THEIR MEDICINAL CORRECTION

L.P. SVIRIDKINA, S.G. TOPOROVA, S.A. ALABINA

Russian Gerontological Scientific Clinical Center, Moscow, Russia

PURPOSE

To compare age-related changes of lymphatic drainage (LD) rate with the activity of lipid peroxidation (LPO) in norm and in case of exogenous intoxication (EI) and to show possibilities of their medicinal correction.

METHODS

By using 300 narcotized white mice aged 3, 6 and 20 months we determined: rate of mesentery LD by the time of complete disappearance of the introduced into it marker – 0.002 ml of 2% Evans blau solution under vital microscopy; LPO activity by the level of malon dialdehyde (MDA), determined by the test with tiobarbiturate acid; hematologic index of intoxication (HII), calculated according to the data of clinical peripheral blood analysis. Parameters were registered in healthy mice; with four-chloride carbon EI (0.3 ml/kg of CC14 intramuscularly for 5 days); after introduction to mature and old animals against EI background of preparations with proved lympho-stimulating activity: mexidolum (2.5 ml/kg i/m) and chophytol (with drinking water 0.2 ml/kg).

RESULTS

It was found that with aging in mice, LD slowed-down 1.4 times in months 3-6, and 1.2 times between months 6-20; MDA level increased in blood serum 7.1 times in 3-6, 1.2 times by month 20; HII increased 5 times in 3-6 months, 2.3 times by month 20 ($p < 0.001$). EI stimulated MDA increase 1.5 times irrespective of age, LD slowed-down 1.3 times and HII grew 3 times in mature mice and 1.4 and 4.3 times in old animals ($p < 0.001$). Administration of mexidolum with chophytol to mature and old mice with EI caused tissue LD acceleration 1.5 and 1.1 times, HII decrease 1.9 and 2.9 times correspondingly ($p < 0.001$). Direct correlation of LD slow-down, increase of MDA concentration and HII values both in norm and with EI ($r =$ from +0.65 to +0.99, $p < 0.001$) was observed.

CONCLUSIONS

Increase of HII values and of LPO intensity was observed in white mice, mostly expressed from 3 to 6 months of age, testifying to the fact that age-related LD slow-down was accompanied by endogenous intoxication. CC14 influence stimulated these changes, especially in old animals. Correlation among LD slow-down, growth of LPO intensity and of HII values with EI as well as possibility of their prevention in mature and old mice by mexidolum and chophytol administration confirmed pathogenic role of age-related LD inhibition in tissues with EI development.

Paper presented to the XXXV Congress of European Society of Lymphology - Paris 2009.

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Presidente della Sessione "Pour une approche raisonnée du traitement opératoire de l'insuffisance veineuse profonde en 2010": Prof. Oscar Maleti

Relazione "L'indication du traitement du reflux veineux profond: limitée aux ulcères rebelles?": Prof. Oscar Maleti

Relazione "Les techniques chirurgicales mixtes dans l'ischémie critique du diabétique": Prof. Oscar Maleti,

Prof. Marzia Lugli

Relazione "Quelles investigations avant chirurgie veineuse profonde?": Prof. Marzia Lugli

Relazione "Laser 980: standardisation des diamètres de la veine avant laser": Prof. Marzia Lugli

Relazione "Intérêt et échographie dans les lipodystrophies": Dott. Elena Righi

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23rd International Congress of Lymphology

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23rd International Congress of Lymphology



Welcome to Sweden and the 23rd International Congress of Lymphology!

Dear Colleagues and Lymphologists!

The Department of Plastic and Reconstructive Surgery at Malmö University Hospital, Sweden, is honoured to organize the 23rd International Congress of Lymphology in cooperation with the Faculty of Medicine at Lund University, and the Swedish Lymphology Association. Problems related to the lymphatic system are central issues for us, and one of our main focuses is the development of surgical techniques related to lymphology.

Olof Rudbeck [1630-1702], a Swedish scientist, published his first treatise *De Circulatione Sanguinis* in 1652, at the age of 22 years only, and he actually became the first one to describe the delineation and function of the lymphatic system in *Nova Exercitatio Anatomica*, which he published one year later. With this historical perspective in mind, we are enthusiastic about hosting the 23rd International Congress of Lymphology in Sweden. We are also proud of being entrusted with the task of arranging the prestigious congress in the city of Malmö. In fact, Malmö connects on to another pioneering scientific work in the field of lymphology performed by Thomas Bartholin [1616-1680], who was active in the nearby capital of Denmark, Copenhagen.

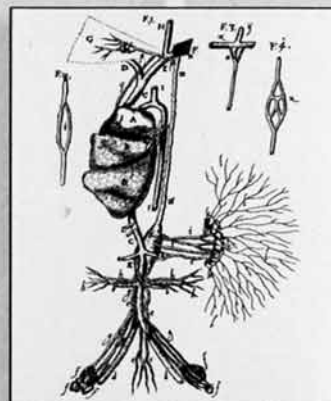
In 2011, from September 19 to 23, the most renowned scientists from all over the world will gather in Malmö to present and debate their front line knowledge and experiences in the various fields of lymphology. This will assure for an interdisciplinary and all-round illumination of the lymphatic system, its pathophysiology, and the state-of-the-art of different treatment regimes. Moreover, at the end of the summer but before fall, September is an excellent time of the year to visit Sweden.

We look forward to seeing you all in Malmö on this very special occasion. Please contact us for any additional information or suggestions that can make your stay even more pleasant in our dynamic and beautiful city.

On behalf of the Organizing Committee,



Håkan Brorson, MD, PhD
Congress President



Turning Torso, a 190 m tall
building for residents.
Photo: Pierre Mens

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23rd International Congress of Lymphology

Program outline

Monday September 19

Registration opens

Tuesday September 20

Welcome reception

Wednesday September 21

Optional social evening,
Tivoli Gardens in Copenhagen

Thursday September 22

Congress dinner

Friday September 23

Congress ends at noon



*Tivoli Amusement Park
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Photo: Tivoli*



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