European Journal of Obstetrics & Gynecology and Reproductive Biology 241 (2019) 35–41

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Endermology treatment for breast cancer related lymphedema (ELOCS): Protocol for a phase II randomized controlled trial

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ARTICLE INFO

Article history:
Received 17 May 2019
Accepted 24 July 2019

Keywords:
Breast cancer
Lymphedema
Endermology
Intensive decongestive treatment

ABSTRACT

Objectives: Secondary lymphedema is a serious and debilitating condition, which may cause a range of cutaneous, infectious and joint complications with major psychological and social consequences. There is no curative treatment available. Initial symptomatic treatment includes Intensive Decongestive Treatment (IDT), which involves the use of multi-layered compression bandages, along with manual lymph drainage, physical exercise and skin care. IDT leads to an average decrease in limb volume of 20–40%, when compared to the contralateral limb. A better reduction may be obtained through the use of new adjuvant techniques, of which endermology is an example. The aim of this phase II study is to validate an IDT protocol combining endermology with standard of care in breast cancer related lymphedema.

Study design: A standardised care protocol was proposed by the University Hospital of Toulouse's Lymphology team for the treatment of upper limb lymphedema after breast cancer surgery using Cellu M6 (LPG) Endermologie over 30 min. Every patient benefitted from IDT over 5 consecutive days, within the multidisciplinary Lymphology unit. Patients were randomised into three arms as follows: Arm 1: IDT for 5 days with bandages + manual lymphatic drainage. Arm 2: IDT with bandages + manual lymphatic drainage + Cellu M6 for 5 days. Arm 3: bandages + Cellu M6 for 5 days. During the study, patients will be followed-up for a period of 6 months.

Use of LPG's Cellu M6 in combination with IDT may improve upper limb volume reduction compared with standard of care. By improving breast cancer related lymphedema, we expect to minimise further fluid build-up and to improve skin care, thus reducing the number of consultations and hospital admissions caused by this condition. The results of the present research protocol are expected to promote evidence supporting the use of endermology in the field of lymphology.

Introduction

Current standard of care for secondary lymphedema involves physical therapy including the use of multi-layered short stretch compression bandages during the intensive phase, followed by compression sleeves for the maintenance phase [1,2]. The exact strategy has to be personalised according to the patient's needs. A holistic and multidisciplinary approach is recommended. Several different treatment methods exist for increasing lymphatic and venous circulation, reducing the oedematous volume, conserving/restoring the aesthetic appearance of the affected limb, and preventing complications [3,4].

International consensus states that several treatment methods should be used to reduce the volume of oedema, and subsequently to ensure that this volume is kept as low as possible [5]. Whichever treatment method is chosen, optimal care of secondary lymphedema

Abbreviations: EV, Excess volume; VL, Volumes limb; VH, Healthy limb; EVD, Excess volume on day; ISL, International society of lymphology; IDT, Intensive decongestive treatment.

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https://doi.org/10.1016/j.ejogrb.2019.07.040
0301-2115/

is usually carried out in two separate phases. The first "intensive" phase aims to reduce the volume of lymphedema, and the second "maintenance" phase aims to maintain the volume reduction in the long term. These 2 phases aim to reduce lymphatic disease progression, reduce the probability of infections and improve patient's quality of life [5,6]. Julia R. Rodrick carried out a literature meta-analysis between 2004 and 2012 [7], critically evaluating complementary, alternative and other decongestive treatments for lymphedema. There were a limited number of randomised controlled trials which looked specifically at lymphedema. Objectively measured outcomes were often missing. Most of the studies had sample size smaller than 50 patients. None of the adjuvant treatment methods analysed proved statistically significant efficacy and none was ranked as being "recommended for practice." This study demonstrated the importance of evaluating new techniques in order to improve lymphedema care.

Non-surgical endermology was created at the beginning of the 1980s by LPG System. It works by softly stimulating cutaneous and sub-cutaneous tissue, using the principle of aspiration, roll-in and roll-out. It allows connective tissue changes to be treated for aesthetic and therapeutic purposes, using mechanical- transduction (activating lipolysis, stimulating adipocytes through the use of ß receptors provoking the release of fat cells, stimulating fibroblasts in order to generate collagen and elastin, decompartmentalising fatty tissues and acting on the septas (cellulite appearance) [8]. LPG Endermologie is a FDA-cleared massage treatment, frequently used in cosmetic dermatology. However, it may also be used for treating burns and scars [9,10]. Pilot studies carried out with relative small sample sizes have demonstrated the possible role of the LPG method in the treatment of lymphedema [11–13].

No scientific evidence exists to justify Cellu M6's popularity amongst physiotherapists in the treatment of lymphedema. There is also no clear instruction for its use. The present randomised study protocol aims to provide a first estimation of success rate and tolerance of LPG Endermologie treatment, Cellu M6, in combination with standard care in reducing breast cancer related lymphedema (BCRL) volume. This study is conducted in a multidisciplinary team approach with a dedicated lymphedema care protocol.

Methods

The RCT protocol used the recommended CONSORT guideline to report on the following items [14].

Trial design

The ELOCS trial is an open-labelled phase II, single centre, randomised (n = 93) trial with three parallel, unblinded arms. Outcome measures will be treatment tolerance and efficacy (BCRL volume reduction) and quality of life [Fig. 1]. The study will take place in the Lymphology unit of the Vascular Medicine department in the University Hospitals of Toulouse in France.

Clinical details and circumference measurements will be taken at the beginning and end at the end of the 5-day treatment. Follow up visits with the vascular physician will take place on days 90 and 180. Clinical details and circumference measurements will also be taken during these visits.

Limb volume will be obtained by carrying out circumference measurements at regular distances (every 5 cm). If the limb sections

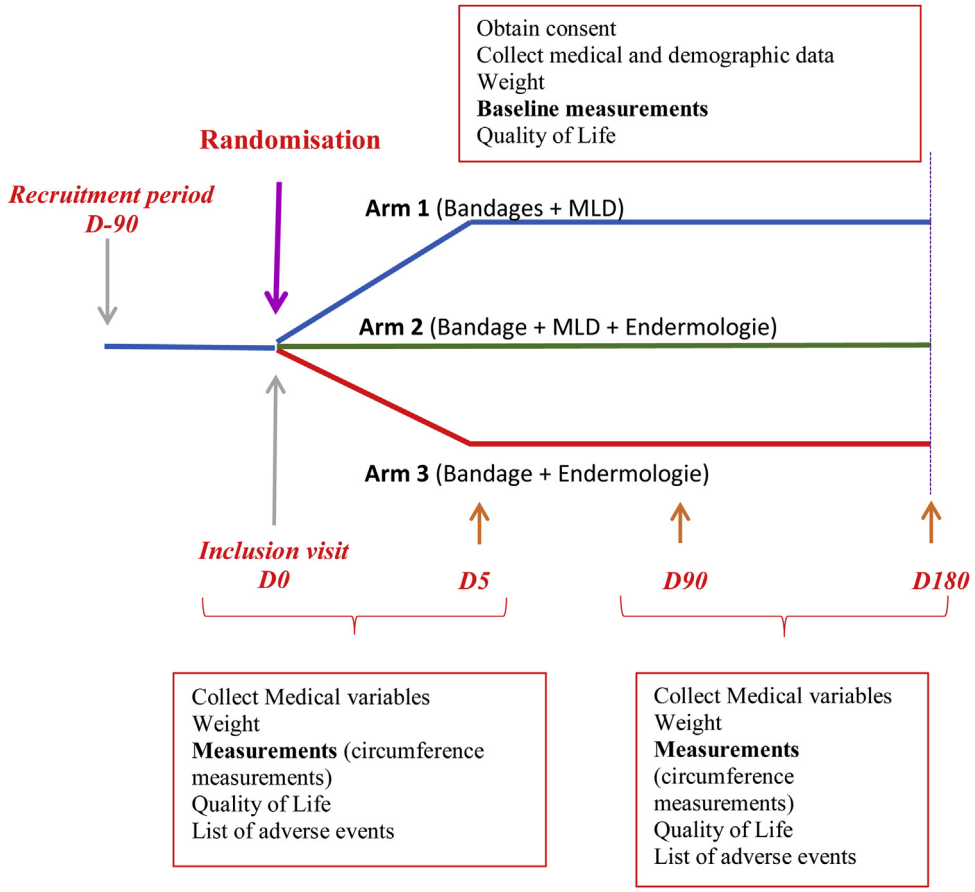

Fig. 1. Overview of the different assessments and their timing in the ELOCS trial. (MLD: manual lymphatic drainage).

are treated as cones, these measurements will give us a volume in ml, as per the following formula [Fig. 2]: H (C2 + Cc + c2) / 12π (C = large cone circumference, c = small cone circumference; H = distance between measurements; π = 3.14) [15,16]. This calculation is reliable and reproducible for the upper limbs [17,18]. The excess volume (EV) will be calculated as the difference between the volumes of the affected limb (VL), and the healthy limb (VH). It is expressed as a percentage: EV = [(VL-VH) / VH] x100.

The reduction in excess volume is the difference between the excess volume on day 5 (EVD5) and that on day 0 (EVD0). It is calculated as follows: [(EVD5 – EVD0) / EVD0] x 100. For the primary objective, a reduction in excess volume of 30% was considered to be significant. This is because IDT allows reductions of 20–40% to be achieved.

The ELOCS trial has been approved by the Ethical Committee of the University Hospitals of Toulouse (main Ethical Committee) on June 19th 2015. The study has been registered in clinicaltrials.gov (NCT02506530) on July 16th, 2015. The inclusion of patients started in January 2016. Total recruitment of all patients has now been achieved and the study follow-up is ongoing.

Randomisation and allocation sequence generation

Randomisation will be carried out by the Clinical Research Methodological Support Unit (USMR) of University Hospitals of Toulouse at the beginning of the trial. The arms will be of equal size (31 patients per arm). Randomisation will be carried out through the use of random blocks, using a ratio of 1:1:1. The randomised list will be sent to the person responsible for pharmacovigilance. Upon recruitment, the investigating physician will open a randomisation envelope. This will give each new recruit a personal identifier and will assign them to an arm. Three visits are planned about monitoring data performed by two clinical research associates.

Participants

Recruitment will be carried out in the Vascular Medicine and Gynaecological Surgery departments in the University Hospital Toulouse Rangueil and in the Toulouse University Institute Cancer – Oncopole. The investigator physician (Dr J. Malloizel-Delaunay) is responsible for obtaining the written informed consent of the patient.

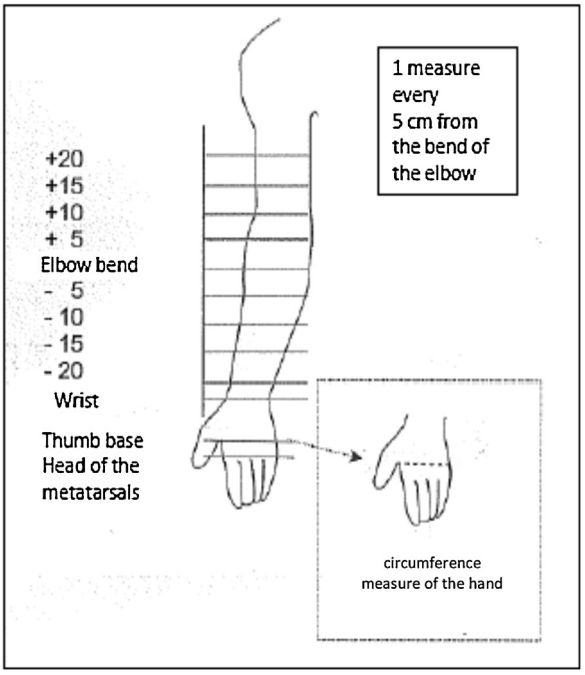

Fig. 2. Standardisation of circumference measurements.

Inclusion criteria include: female patients, over 18 years of age, suffering from stage 2 lymphedema secondary to breast cancer, as per the ISL classification system [19], of over 6 months' evolution, with a greater than 10% difference in upper limb volume, who underwent axillary node dissection, who have been hospitalised for standard intensive decongestive treatment (IDT) for 5 days (bandages + manual lymphatic drainage), with health insurance and who have signed the informed consent form.

Exclusion criteria include: pre-existing primary lymphedema, associated upper limb venous insufficiency, upper limb obliterating arteritis, bilateral lymphedema, relapsed breast cancer, a separate cancer under treatment, decompensated heart failure, pacemaker, acute infection (cellulitis, erysipelas, lymphangitis), acute deep vein thrombosis, upper limb skin atrophy, bullous dermatosis, presence of external part of subcutaneous osteosynthesis material in the upper limb to be treated, shoulder hyperalgesia, inability to follow trial protocol, pregnancy, breastfeeding or if the patient is under the protection of the law (guardianship, curatorship or legal guardian).

Assessments

The Fig. 1 gives an overview of the different assessments and their timing in the ELOCS trial.

Primary outcomes

We designed this study to validate a protocol of care combining endermology and standard of care with IDT.

The primary outcome of this study is to evaluate the proportion of patients treated successfully (success rate). Success is defined as a reduction in upper limb excess volume $\geq$ 30% on day 5. Three types of treatments will be proposed, depending on patient's treatment arm: arm 1: standard IDT for 5 days (bandages + manual lymphatic drainage), arm 2: standard IDT for 5 days (bandages + manual lymphatic drainage) + Cellu M6 and arm 3: bandages + Cellu M6 for 5 days.

Secondary outcomes

Secondary outcomes will be evaluated for each arm on day 5, and at 3 and 6 months after the start of treatment. Outcomes measured will include: comparison of final lymphedema excess volume on day 5 in each arm, the evolution of the excess fluid during the study follow-up, the increase in excess fluid after day 5 (measured at 3 and 6 months as the difference between the volume of the affected limb, and the healthy limb, expressed as a percentage), the feasibility of applying the care protocol developed for the Cellu M6, the clinical features of the lymphedema and its evolution (range of motion, limb pain, limb heaviness, discomfort when using the limb), breast cancer specific quality of life, overall quality of life as measured by the EQ-5D questionnaire and its evolution, adverse local and regional effects of IDT (bandages, Cellu M6, manual lymphatic drainage), especially friction wounds, blisters, lymphorrhea, skin intolerance, sores etc. Adverse events due to the disease (locoregional or distant recurrence, and time frame), local and regional adverse events due to lymphedema (notably infections), maintenance treatment methods after 5 days of IDT (in association to class III compression garment, maintenance treatment is personalized according to the patient's needs with night compression garment, manual lymphatic drainage,

pressotherapy, self-bandaging, Cellu M6 sessions and adapted physical exercises), the proportion of patients requiring hospital admission or sick-leave due to lymphedema (number of participants as well as the total number of days).

Interventions

The endermology protocol is shown in Fig. 1 and Table 1.

- *Study procedure with the LPG system.*

The LPG system is a medical device, which allows the user to softly stimulate the cutaneous and sub-cutaneous tissue, using the principle of aspiration-roll in-roll out. The INTEGRAL I model is a device aimed for therapeutic use. It obtained CE marking in September 2009. Treatment with Cellu M6 will be carried out every day of the IDT (days 1 to 5). It will be carried out by the lymphology unit's physiotherapists [Fig. 3]. These physiotherapists have benefited from endermology expert training. The session will last 30 min and will precede the application of bandages, as suggested during preliminary studies [13].

- *Intensive Decongestive Treatment*

Care within the Lymphology unit is all-encompassing and multidisciplinary. It includes medical, nutritional, educational and psychological care as well as physiotherapy.

IDT is carried out every day, over the course of 5 consecutive days. Before every treatment, the patient will be given an in-depth examination. Measurements will also be taken of the circumference and range of motion of the upper limbs.

The first stage of the treatment involves manual lymphatic drainage, carried out by the masseuse-physiotherapist, using the Leduc technique [20]. It lasts 30 min. The second stage involves skin care. The aim of this treatment is to preserve the skin barrier, thus avoiding infections and induration. The physiotherapist uses an emollient cream (Cold Cream).

The third stage involves the application of compressive bandages, to be worn at all times between sessions. This is done by the physiotherapist, using dry, short stretch Rosidal K bandages, as well as coverings such as N/N foam band, or MOBIDERM bands, varico or cotton. The fourth stage is comprised of physical exercises carried out with the bandages. These include suppleness exercises,

Table 1
Cellu M6 protocol description.

Before using this protocol a cover (jersey type) is placed on the limb and thorax.
For lymphedema treatment, select the ROLL menu:
- Roll Up for the oedema
- Roll in for fibrotic areas, underarm scars and adhesions and for drainage: scapular area in relation to the sub-clavian zone and at the flexor retinaculum of the wrist (highly vascular area).

The protocol used:

- Head used:

Tête TR50: for dorsal, lateral and anterior thorax and upper limb.
Tête TML30: for the hand and fragile/scarred skin
- Setting the frequency:

16 for all circular and longitudinal paths.
- Setting the roller speeds: 1 speed at 80-40
- Setting the cycles 80
- Setting the intensity:

For tête TR50: between 1 or 1.5 or 2 or 2.5, depending on the aspiration force used and the patient's tolerance.
For tête TML30: between 2.5 or 3 or 3.5 depending on the aspiration force used and the patient's tolerance.

1st protocol time	The patient must be in lateral decubitus position, on her healthy side
	Trace out 2 back and forth paths:
	On the 3 dorsal paths
	on the descending dorsal path, towards the sacro-iliac joint
	On the descending lateral path, towards the navel
	On the anterior path, under the breast
	On the anterior path, above the breast
	Trace out 1 longitudinal path from the sacroiliac joint, as far as the armpit
	In Roll In "swing" mode. Repeat 4 times
	At the axillary fold
	At the scapula
2nd protocol time	The patient must be in dorsal decubitus:
	At the shoulder: Trace out 4 circular paths
	On the arm, divided into 3 parts: proximal, medial and distal
	Trace out 4 circular paths
	Trace out 4 longitudinal paths: internal, anterior, external and posterior along the circumference of the arm
	On the forearm, divided into 3 parts: proximal, medial and distal
	Trace out 4 circular paths
	Trace out 4 longitudinal paths: internal, anterior, external and posterior along the circumference of the forearm
	In Roll In "swing" mode. Repeat 4 times
	At the flexor retinaculum of the wrist
	On the back of the hand
	For the hand: tête TML30
	Trace out 3 transversal paths along the interior of the palm of the hand, from the hypothenar eminence, as far as he thenar eminence.
	Trace out 4 longitudinal paths: internal, anterior, external and posterior along the circumference of the arm from the wrist as far as the shoulder
	Finish on the thorax using a transversal path, which goes above and below the breast

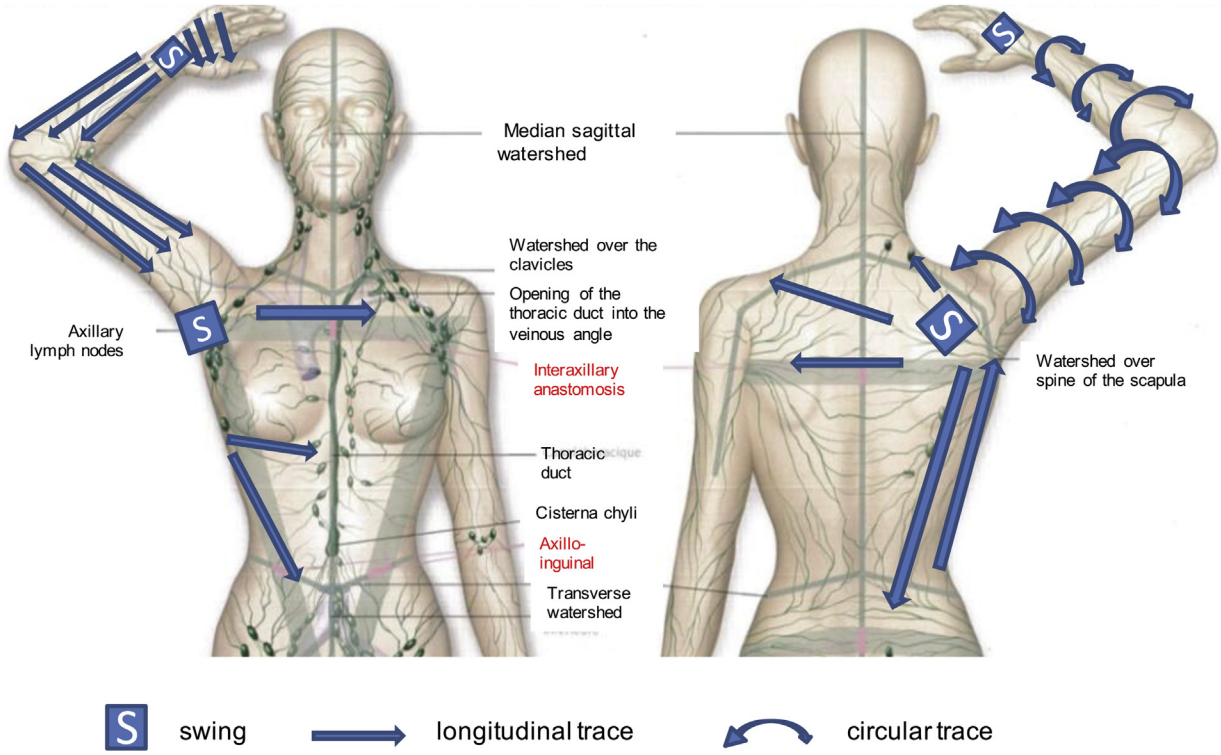

Fig. 3. Cellu M6 application areas with longitudinal and circular traces (from Millard Frederick P. Millard, ed. Sully. Anatomie appliquée du système lymphatique, 2014).

resistance work and aerobic exercises. The exercises are supervised by the physiotherapist, and last for 30 min. The fifth stage involves complementary care, including therapeutic and self-care education.

During the 5 days intensive phase (excluding compression bandage), the average of care is 3 h per day, (ie 15 h per week associating skin care, education, MLD and endermology . . .). The duration of maintenance phase is 6 months.

If a patient cannot commit to full intensive treatment because of co-morbidities, modified intensive treatment will include all the elements of the intensive regime but tailored to patient's needs.

- *Maintenance phase*

After the IDT, all patients have a maintenance treatment for 6 months (compression sleeves and garments with or without a glove or gauntlet, physiotherapy (endermology or MLD), skin care and auto-self compression).

Sample size calculation

The sample size calculation in this randomized study (ratio 1:1:1) was carried out using a Fleming single stage procedure [21] and the following hypotheses: the largest response probability $P_0 = 50\%$ (we consider that a response rate below this value does not justify continuing investigations with this line of treatment regimen), the null hypothesis H_0 states that the success rate is inferior to the largest response probability, the smallest response probability, $P_1 = 75\%$ (we consider that a response rate above this value warrants continuing investigations with this line of treatment regimen), hypothesis H_1 states that the success rate is higher than the smallest response probability. Probabilities of making Type I and Type II errors are $\alpha = 5\%$ and $\beta = 10\%$ (corresponding to 90% power), respectively.

Under these hypotheses, 31 patients are required in each experimental arm (arms 2 and 3). The method will be considered to be of interest if the treatment of at least 21 out of 31 patients is successful [22].

Statistical methods

Statistical analysis will be carried out on the anonymised patients' database, after it has been cross checked, validated and frozen, by the Clinical Research Methodological Support Unit at Toulouse University hospital.

An initial description of the arms will be carried out. Categorical variables will be described using frequencies and percentages. Continuous variables will be summarized as mean and standard deviation when the distribution is normal and as median and interquartile range if the distribution significantly depart form normality. Minimal and maximal values of the continuous variable will be provided.

To answer to the principal outcome of this study, the reduction in lymphedema excess volume on day 5 will be compared in each arm the success rate will be estimated in each arm (it will be defined as the percentage of patients who achieve a reduction of $\geq$30% in excess volume by the end of treatment on day 5).

To answer to secondary criteria, distribution of continuous variables will be described in each treatment arm (mean, median, standard deviation and interquartile range, as appropriate). Change from day 0 will be assessed first as the difference between the measurement obtained on day 0 and those carried out on day 5, at 3 months and at 6 months (with a particular attention to quality of life). Change from day 0 will also be assessed as a percent change from day 0. Distribution of categorical criteria will be described against treatment arm.

Statistical analysis will be performed on anonymous data, after verification and stop the database, by the USMR of Toulouse University Hospital.

Discussion

This is the first phase II, single centre, randomised trial with three parallel unblinded arms, evaluating the proportion of patients treated with endermology who achieve a reduction of excess fluid volume of the upper limb. Intensive phase's optimal duration seems not currently standardized. The most substantial lymphedema reduction has been reported within the first 3 days of intensive decongestive therapy [23]. The effect of endermology might therefore appear at the end of the 5 planned sessions.

Lymphedema is a possible sequela of cancer [24]. It is a chronic, disabling condition, which reduces the quality of life of the sufferer [25]. It has a large social cost, both due to its psychological and physical effects, as well as its impact on people's ability to work [25,26]. Care optimisation is of fundamental importance for achieving early and adapted cancer rehabilitation.

Use of LPG's Cellu M6 in combination with IDT may achieve a greater upper limb volume reduction compared with IDT standard care. This would lead to a lessening in the heaviness felt by the patient due to their lymphedema [26,27]. Volume reduction also improves the patient's psychological and social well-being. The present study will be able to provide evidence about the benefit of the association of endermology with manual lymphatic drainage and also to evaluate the safety and tolerability of endermology compared to MLD.

Moreover, endermology should also relax the sub-cutaneous tissue, in particular the scar tissue associated with axillary adhesions and thus increasing the shoulder's range of motion. This would result in greater autonomy for the patient and it would also optimise their treatment, hopefully leading to a reduction in complications. Further studies should have the potential to investigate the benefit of endermology in patients with severe BCRL associated with axillary adhesions. Scientific justification is required for the use of endermology in the field of lymphology. The present study will evaluate whether it is feasible and worthwhile to carry out a phase III efficiency trial.

Ethics approval and consent to participate

The trial was registered with clinicaltrials.gov on July 16th, 2015.

Ethics approval and signed informed consent of participants is required.

The ELOCS trial has been approved by the Ethical Committee of the University Hospitals of Toulouse (main Ethical Committee) on June 19th, 2015.

Funding

This study was supported by a local grant from the University Hospital Toulouse, local grant 2014.

Author's contribution

Dr Julie Malloizel-Delaunay (MD, principal investigator): study concept and design, manuscript preparation, manuscript review, inclusions of patients. Dr Elodie Chantalat (MD): manuscript preparation, manuscript review. Pr Vanina Bongard (MD, PhD): study concept (statistical part), manuscript preparation, manuscript review. Pr Benoit Chaput (MD, PhD): manuscript preparation, manuscript review. Barbara Garmy-Susisni (PhD): manuscript review. Dr Alexandra Yannoutsos (MD, PhD): manuscript preparation, manuscript review. Dr Charlotte Vaysse (MD, PhD, co-investigator): study concept and design, manuscript preparation, manuscript review, inclusions of patients.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank the multidisciplinary team of Lymphology Department of the Toulouse University Hospital (physiotherapists: H. Trémas, Y. Smati, N. Elkamil; therapeutic education nurse: K. Faucher, dietician: K. Espitalier, psychologist: H. Bengrouba) and the Sport Medicine Department of the Toulouse University Hospital, France (Pr D. Rivière).

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