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Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphoedema (EFforT-BCRL trial)

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ABSTRACT

Objectives: Lymphoedema is a dreadful complication following breast cancer therapy. According to the International Society of Lymphology, the consensus treatment for breast cancer-related lymphoedema (BCRL) is the decongestive lymphatic therapy. This is a two-phase treatment and combines different treatment modalities including skin care, manual lymphatic drainage (MLD), compression therapy and exercise. However, the additional effect of MLD is debated since pooled data only demonstrated a limited non-significant additional value. A possible explanation is that in previous studies MLD has been applied blind, without knowledge of patient-specific lymphatic routes of transport. In addition, the MLD hand manoeuvres used by the therapists in previous studies, possibly did not optimally stimulate lymphatic transport. Recently, near-infrared fluorescence imaging has been introduced to visualise the superficial lymphatic network which allows MLD at the most needed location. The aim of the present study is to determine the effectiveness of the fluoroscopy-guided MLD, additional to the other parts of the decongestive lymphatic therapy and compared to the traditional or a placebo MLD, in the treatment of BCRL.

Study design: A three-arm double-blinded randomised controlled trial will be conducted in different university hospitals in Belgium. Based on a sample size calculation, 201 participants with chronic BCRL stage 1 or 2 of the arm or hand, with at least 5% difference between both sides (corrected for hand dominance) need to be recruited. All participants receive the standard treatment: skin care, compression therapy and exercises. The intervention group additionally receives fluoroscopy-guided MLD. One control group additionally receives the traditional 'blind' MLD and a second control group receives a placebo MLD. All subjects receive 3 weeks of daily intensive treatments and 6 months of maintenance treatment. Follow-up period is 6 months. The primary outcomes are the reduction in lymphoedema volume of the arm/hand and the change in stagnation of lymph fluid at level of the shoulder/trunk.

Introduction

Lymphoedema is an embarrassing and dreadful morbidity after breast cancer treatment. The incidence of breast cancer-related lymphoedema (BCRL) of the arm is 16% [1]. Lymphoedema does not only induce physical impairments such as swelling, heaviness

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and problems with performing household activities and mobility [2], but also psychosocial problems [3].

According to the recommendations of the International Society of Lymphology (ISL), lymphoedema needs to be treated with decongestive lymphatic therapy [4]. This is a two-stage treatment programme. During the first or intensive phase, lymphoedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimise the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.

Due to the significantly improved screening and treatment modalities for breast cancer over the last few years, survival rates are growing resulting in a prevalence rate of BCRL which is still increasing as well [5]. In Belgium, almost all lymphoedema patients receive MLD as part of the physical treatment, which can be time-consuming for patients and entails a big financial cost for the patient as for the Health Care system [6]. However, a meta-analysis, including 6 randomised controlled trials (RCT's), and a Cochrane systematic review have questioned the effectiveness of MLD [7,8]. The meta-analysis showed an overall additional benefit of MLD to the treatment of BCRL of 75 ml, while the systematic review revealed that the individual contribution of MLD was limited to 7% [7,8]. Two recent RCT's were unable to demonstrate an additional effect of MLD to decongestive lymphatic therapy [9,10].

A possible explanation why MLD according to the method applied in previous studies, has a rather small benefit in addition to the other parts of decongestive lymphatic therapy, is that MLD is applied in an inefficient or 'blind' way. This method of MLD is further called 'traditional MLD'.

After dissection of the axillary lymph nodes, whether or not in combination with radiotherapy, the lymphatic system of the upper limb is damaged. Lymph nodes are removed and often fibrosis of the superficial lymphatic system follows [11,12]. As a result, reverse flow of lymph fluid coming from collecting vessels and going through precollecting vessels in direction of the dermal capillaries, can occur. This dysfunctional phenomenon is called dermal backflow [13]. Moreover, rerouting of lymphatic drainage via lymph collaterals and dermal capillaries, also called dermal rerouting, has been described in patients with lymphoedema [14,15]. This rerouting is patient-specific. Therefore, it is proposed that the traditional or 'blind' MLD needs to be abandoned and a tailored approach needs to be established. Near-infrared fluorescence imaging or lymphofluoroscopy can aid to apply a more efficient MLD. During this investigation, diluted Indocyanine Green (ICG) is injected intradermal in the hand; it visualizes the superficial transport of lymph from the hand up to the axilla and it demonstrates alternative pathways towards other lymph nodes [16].

A second possible explanation why traditional MLD has not proven to be effective, is that the therapist does not optimally stimulate lymphatic transport. The resorption of lymph capillaries has to be performed with the thumb (instead of with the hand in the traditional MLD, which gives a lower pressure). In addition, gliding (compared to no gliding) is hypothesised to be more effective to enhance lymphatic transport [17]. The physiological effect of one session of fluoroscopy-guided MLD was demonstrated in patients with BCRL [17,18]. Whether the application of different sessions of fluoroscopy-guided MLD has a clinical and long-lasting effect on the lymphoedema, superior to the traditional MLD, has yet to be established.

Further, clinical experience revealed that patients report a positive subjective feeling after MLD. Whether this is a real effect rather than a placebo-effect, needs to be investigated as well.

The objective of this trial is to examine the effectiveness of fluoroscopy-guided MLD versus traditional MLD and versus placebo MLD, applied as part of the decongestive lymphatic therapy, for the treatment of BCRL.

Methods

The RCT protocol used the recommended CONSORT guideline to report on the following items [19].

Trial design

The EFforT-BCRL trial is a multicentre double-blind three groups RCT. Fig. 1 gives an overview of the participant flow. All participants (n = 201) receive an intensive treatment lasting 3 weeks and a maintenance treatment for 6 months. Additionally, they are followed up for another 6 months. All participants receive a standard treatment consisting of skin care, compression therapy, exercises and information. Only the MLD differs among the three groups: the intervention group receives a fluoroscopy-guided MLD, control group one receives the traditional MLD and control group two receives a placebo MLD. The participants are assessed before the start of the trial, after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of additional follow-up.

All treatments and assessments are performed at the department of Physical Medicine and Rehabilitation (treatment and clinical assessment) and at the department of Vascular Surgery (lymphofluoroscopy) of the University Hospitals of Leuven, at the Multidisciplinary Breast Clinic in the Antwerp University Hospital, at the Lymphology Clinic in Saint-Pierre University Hospital in Brussels and at the Centre of Oncology in General Hospital Groeninge in Kortrijk.

The EFforT-BCRL trial has been approved by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) and received positive advise from the Ethical Committees of all other participating centres (CME reference S58689, EudraCT Number 2015-004822-33). The study has been registered in clinicaltrials.gov (NCT02609724).

Randomisation and allocation sequence generation

All participants are allocated to one of the three groups. The random allocation sequence is computer-generated. Randomisation is performed by using 6-size permuted blocks. The allocation to the groups is concealed and performed by an independent physical therapist. The sequence of randomisation is determined by the participant's identification number, which he/she receives after inclusion in the study.

Blinding

All participants are blinded for the allocation to one of the three MLD groups.

Additionally, all clinical as well as fluoroscopic assessments are performed by investigators who are blinded for the allocation of the patients to the treatment groups. The therapists are blinded to participants' data, but are aware of the treatments provided to the three different groups.

Participants

Participants are recruited from three university hospitals and one general hospital in Belgium: University Hospitals of Leuven (n = 90), Saint-Pierre University Hospital in Brussels (n = 20), Antwerp University Hospital (n = 51) and General Hospital

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