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Research

Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial

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KEY WORDS

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ABSTRACT

Question: What are the short-term and long-term preventive effects of manual lymph drainage (MLD), when used in addition to information and exercise therapy, on the development of lymphoedema after axillary dissection for breast cancer? **Design**: Randomised controlled trial with concealed allocation, blinded assessors and intention-to-treat analysis. **Participants**: Adults undergoing unilateral dissection for breast cancer were recruited, with 79 allocated to the experimental group and 81 to the control group. **Intervention**: The experimental group received guidelines about prevention of lymphoedema, exercise therapy and MLD. The control group received the same guidelines and exercise therapy, but no MLD. The interventions in both groups were delivered for 6 months. **Outcome measures**: The primary outcome was cumulative incidence of arm lymphoedema defined in four ways ($\geq$ 200 ml, $\geq$ 2 cm, $\geq$ 5%, and $\geq$ 10% increase), which represent the difference in arm volume or circumference between the affected and healthy sides compared with the difference before surgery. Secondary outcomes included point prevalence of lymphoedema, change in arm volume difference, shoulder range of movement, quality of life and function. **Results**: Incidence rates were comparable between experimental and control groups at all follow-up measurements. Sixty months after surgery, the cumulative incidence rate for the $\geq$ 200 ml definition was 35% for the experimental group versus 29% for the control group (RR 0.89, 95% CI 0.51 to 1.54, $p = 0.45$); for the $\geq$ 2 cm definition 35% versus 38% (RR 0.93, 95% CI 0.59 to 1.45, $p = 0.73$); for the $\geq$ 5% definition 68% versus 53% (RR 1.28, 95% CI 0.97 to 1.69, $p = 0.08$) and for the $\geq$ 10% definition 28% versus 24% (RR 1.18, 95% CI 0.66 to 2.10, $p = 0.57$). The secondary outcomes were comparable between the groups at most assessment points. **Conclusion**: Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the short and long term. **Trial registration**: Netherlands Trial Register NTR 1055. **[Devoogdt N, Geraerts I, Van Kampen M, De Vrieze T, Vos L, Neven P, Vergote I, Christiaens M-R, Thomis S, De Groef A (2018) Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. *Journal of Physiotherapy* XX: XX–XX]**

Introduction

Among all cancers, breast cancer is the most frequent type in females. In 2012, 1.7 million women were diagnosed with breast cancer worldwide. Due to the evolution in diagnostic and treatment techniques, the survival rate is increasing.[1] Consequently, complications related to the treatment of breast cancer have gained importance. Lymphoedema is one of the most feared complications. Lymphoedema is caused by a reduced transport capacity of the lymph system (related to the surgery, radiotherapy, or both), sometimes combined with an increase in lymph load (eg, related to infection).[2,3] Lymphoedema can cause functional impairments[4] and psychosocial morbidities,[5] and may lead to diminished health-related quality of life.[6,7]

Although the majority of patients seem to develop breast cancer-related lymphoedema before 12 to 24 months postoperatively,[8,9] breast cancer survivors have a lifelong risk of developing lymphoedema.[10] Incidence rates of lymphoedema vary among studies, with an overall incidence of 21%.[11] Prospective studies have described a cumulative incidence of 10% at 2 years,[12] between 21 and 54% at 3 years,[7] and between 16 and 94% at 5 years post-surgery.[8,12,13]

Lymphoedema can be diagnosed using a wide spectrum of subjective and objective measurement methods. Subjective

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findings include self-report of symptoms of heaviness, pain and swelling, which are moderately reliable.[14,15] The most commonly used measurements of limb volume are the circumference measurement and the water displacement method.[16] The perimeter and volumeter are reliable measurement devices to assess arm circumferences and volumes, respectively.[17,18] A difference of $\geq$ 200 ml or $\geq$ 2 cm compared to the pre-surgical value are frequently reported as lymphoedema.[14,19] However, a study demonstrated the superiority of relative arm size changes (5% and 10%), since they take into account the arm volume of the patient at baseline.[20] The same absolute change of arm volume difference has a greater impact in a patient with low body weight (and a small arm volume) than a patient with high body weight (and a larger arm volume). A frequently occurring complication after lymph node dissection for breast cancer is decreased shoulder range of motion.[21] For people with breast cancer-related lymphoedema, the SF-36 and Lymph-ICF questionnaires are reliable and valid questionnaires for assessing health-related quality of life on the one hand and associated problems in functioning on the other hand.[22,23]

Prevention of lymphoedema is an important issue. By application of manual lymph drainage (MLD) immediately after axillary dissection, development of lymphoedema may be prevented. The aim of this 'preventive MLD' is to stimulate rerouting of the lymphatic system after lymph node dissection and to eliminate accumulated water and proteins out of the interstitial tissue. The randomised controlled trial by Lacomba et al (n = 120) showed that the combination of MLD, exercise therapy and information resulted in a lower incidence of arm lymphoedema than information alone.[24] Yet, the contribution of MLD on the prevention of arm lymphoedema cannot be derived from this study. So far, two randomised controlled trials have investigated the preventive effect of MLD, as a unique treatment modality, additional to another physical treatment.[25] The study by Devoogdt et al (n = 160) found that when MLD was added to exercise therapy and information, it was unlikely to be effective for the prevention of lymphoedema.[26] In contrast, the randomised controlled trial by Zimmermann et al (n = 67) reported that the addition of MLD to information and exercises was effective.[27] The Cochrane systematic review by Stuiver et al investigated 10 aspects of risk of bias in both studies. They concluded that the risk of bias in the trial by Zimmermann was high, whereas the risk of bias in the trial by Devoogdt was moderate.[25] Follow-up was short to moderate and ranged from 6 to 12 months in these studies.[25–27]

The preventive effect of MLD on the development of breast cancer-related lymphoedema in the long term has never been examined. It is important to investigate whether there is a long-term preventive effect because a treatment immediate post-surgery may result in prevention of lymphoedema later on during the postoperative period. This has been shown in the study by Lacomba.[24] Immediately after surgery, participants received nine sessions over 3 weeks of information (control group) or information, exercises and MLD (experimental group). The first participant in that study developed lymphoedema 7 months after surgery and most who developed it did so between 10 and 12 months after surgery. The participants were not followed beyond 12 months. It is important to continue the follow-up beyond 12 months because 20 to 33% of patients with breast cancer who develop arm lymphoedema will do so more than 12 months after surgery.

The above-mentioned study by Devoogdt et al[26] followed participants beyond 12 months after their surgery. The previous publication presented the short-term (up to 1 year) effects of MLD.[26] The aim of the present report is to examine the long-term, preventive effects (up to 5 years after surgery) of MLD.

Therefore, the research question for this trial was:

What are the short-term and long-term preventive effects of manual lymph drainage when used in addition to information and exercise therapy on the development of lymphoedema after axillary dissection for breast cancer?

Method

Design

A randomised controlled trial was performed with concealed allocation, blinded outcome assessment, and intention-to-treat analysis. Participants were enrolled at the time of axillary dissection for breast cancer. After baseline assessment, participants were individually randomised into either an experimental group or a control group. Concealed allocation was achieved by having randomisation performed by a researcher who was not involved in the recruitment and treatments of participants. Four permuted blocks were used to stratify randomisation by body mass index ($\leq$ 25 versus $>$ 25 kg/m^2) and by axillary irradiation (yes/no) because these are the most important risk factors for the development of breast cancer-related lymphoedema.[7,14,28] Post-operatively, participants in both groups were prescribed exercise therapy and provided with information about prevention of lymphoedema. In addition, participants randomised to the experimental group received manual lymph drainage. Participants in both groups were assessed, by a researcher who was unaware of the randomised group allocations, for the development of lymphoedema at 6, 12, 24 and 60 months after their surgery.

Participants, therapists, centre

All patients with operable breast cancer and scheduled for unilateral surgery at the Multidisciplinary Breast Centre of the University Hospitals Leuven between October 2007 and February 2009 were assessed for study eligibility prior to surgery. Only patients with a unilateral axillary dissection levels I, I–II or I–III were included in the study. Patients were excluded if they: had a sentinel procedure on the contralateral side; were physically or mentally unable to participate; were not interested; or had breast cancer metastasis at first diagnosis.

All treatments (information, exercise therapy and MLD) were performed by four therapists. Two of the therapists had undergone MLD training with the Leduc method, and the two other therapists had undergone MLD training with the Vodder method.

Intervention

Both groups

During hospitalisation, participants received the following information about the prevention of lymphoedema: elevate the arm in case of heaviness, avoid lifting heavy objects, use the arm in daily life as normally as possible, avoid limb constriction, avoid extremes of temperature, apply skin care, and avoid an increase in body weight.[29] These guidelines were outlined in a brochure and, when requested, patients could obtain more information during the exercise therapy sessions.

Participants were also prescribed exercise therapy, which was started during hospitalisation with low level mobilising exercises for the hand, elbow and shoulder. After hospitalisation, 30-minute individual exercise sessions were provided at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven. These sessions consisted of: passive mobilisation of the shoulder; stretching and transverse strain of the breast muscles; scar tissue massage; and active mobilising and stabilising exercises.[26] In the beginning, participants were seen twice a week and frequency was gradually diminished to once every 2 weeks, over a total treatment period of 6 months.

A participant who developed lymphoedema (defined as an increase of 200 ml or more in arm volume compared with baseline) in either group had to wear an inelastic bandage. When the

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