ORIGINAL PAPER

Nagoya J. Med. Sci. **79**. 221 ~ 227, 2017
doi:10.18999/nagjms.79.2.221

Multi-center rater-blinded study of early intervention with the Hand Incubator for breast cancer-related lymphedema (the BEAT-EDEMA trial): Proposal of a research protocol

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ABSTRACT

Postoperative lymphedema is considered irreversible once it has developed, and significantly lowers the patient's quality of life. However, lymphatic function has recently been clarified, and it is possible that lymphedema can be cured if early treatment is started. This two-arm randomized clinical trial (UMIN000026124) will prospectively evaluate 24 patients with early-stage breast cancer-related lymphedema at the Nagoya University Hospital and Aichi Cancer Center Hospital. The eligibility criteria will be patients who are diagnosed with stage 0–1 breast cancer-related lymphedema, as defined by the International Society of Lymphology, within 12 weeks after breast cancer surgery. The diagnosis of lymphedema will be confirmed using a bioimpedance spectroscopy device (L-Dex®). Participants will be randomized 1:1 into the intervention and control groups. The physicians and patients will be aware of their group assignment, although treatment efficacy will be evaluated by raters who are blinded to the group assignments. The intervention group will complete grasping exercises in the Hand Incubator device for 4 weeks. The primary outcome will be the change in the affected upper limb's volume after the intervention, as measured using the water displacement method. This study may help establish a standard treatment for postoperative lymphedema.

Key Words: breast cancer, lymphedema, exercise therapy, randomized controlled trial, rater-blinded study

INTRODUCTION

Lymphedema is a common refractory complication that occurs after surgery for various cancers, such as breast, uterine, or prostate cancers, and there is no effective treatment.[1,2] The reported incidence of lymphedema after treatment for breast cancer ranges from a few percent to tens of percent, although this condition does not develop immediately after surgery and can take

Received: March 8, 2017; accepted: April 13, 2017

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months or years to emerge.[2,3] During the 20th century, knowledge of the lymphatic system was extremely scarce and there were no established diagnostic criteria for lymphedema. Thus, the diagnosis was mainly performed using visual inspection, and epidemiological evidence regarding lymphedema occurrence was largely unreliable. However, subsequent elucidation of the molecular mechanism for lymphangiogenesis and the development of diagnostic tools have led to rapid clarification of the pathology of lymphedema that is associated with cancer treatment.[3,4] Although lymphatic vessels have a structure that is similar to that of blood vessels, only lymphatic vessels have an intrinsic pumping mechanism. Unno *et al.* and Modi *et al.* used indocyanine green (ICG) fluorescence lymphography and lymphatic congestion lymphoscintigraphy to confirm that the lymphatic pumping force was reduced in limbs with secondary lymphedema, and that this "lymphatic failure" could contribute to the pathogenesis of lymphedema.[5,6] Bräutigam *et al.* also detected an accelerated rate of lymphatic transport (high lymph volume overload or dynamic insufficiency) in patients with edema, and used lymphoscintigraphy to analyze lymphatic abnormalities in the epifascial and subfascial compartments of patients with a variety of leg edema syndromes.[7] Chakraborty *et al.* have reported that increases in diastolic lymphatic pressure result in increased contraction frequency and phasic contraction strength in the collecting lymphatic vessels, but beyond a certain point the contractile structures begins to fail and the contraction amplitude decreases.[8]

The International Society of Lymphology (ISL) modified the clinical staging criteria for lymphedema in 2013 (Table 1) and added stage 0, which refers to a latent or subclinical condition where swelling is not yet evident despite underlying changes in the lymphatic system.[9,10] The National Lymphedema Network (NLN) is a driving force behind the American movement to standardize treatment for lymphedema, and has also announced that detection of lymphedema at the earliest stage is a key step in preventing or slowing the progression of lymphedema to a chronic and harder-to-treat stage.[11,12] Several other studies have collected cohorts of patients with breast cancer for lymphedema research at major American medical institutions.[13,14,15] These patients underwent surgical treatment for breast cancer and are continuously monitored for lymphatic dysfunctions before and periodically after their surgery. Several randomized controlled trials have also attempted to verify the efficacies of treatments for lymphedema.

Table 1 The modified International Society of Lymphology (ISL) clinical staging of lymphedema (2013)

Stage 0 (subclinical)	Swelling is not yet evident, despite the impaired lymphatic system.
Stage 1	Early fluid accumulation that subsides with limb elevation.
Stage 2	Swelling is constant and does not resolve using elevation, and pitting is evident.
Stage 3	Pitting may be absent, although trophic skin changes have developed.

Subclinical lymphedema can currently be detected using various imaging modalities, such as lymphoscintigraphy, magnetic resonance imaging lymphography, ICG fluorescence lymphography, and bioelectrical impedance analysis (BIA). However, scintigraphy and magnetic resonance imaging are not suitable for regular monitoring because they require large facilities. BIA has been reported as an accurate quantitative method for monitoring the treatment of lymphedema.[16] One bioimpedance spectroscopy device was developed in Australia (L-Dex®, ImpediMed), approved by the American Food and Drug Administration in 2009 as an early diagnostic tool for lymphedema, and has subsequently become widely used. Nevertheless, BIA cannot identify the cause of the

edema or quantitatively evaluate lymphodynamics, because it is an indirect evaluation method that is based on measuring compositional changes in the interstitial fluid. Although ICG lymphography may be an extremely useful tool for diagnosing lymphedema, it has not been approved in any country because of a lack of validation testing.

Clinical research is gradually providing reliable information regarding the treatment of breast cancer-related lymphedema (BCRL). The conventional treatments for lymphedema include manual lymphatic drainage or compression therapy using various instruments, such as bandages, garments, and intermittent pneumatic compression devices, although a 2015 Cochrane review could not confirm the efficacies of these treatments.[17] However, the National Institutes of Health emphasizes the importance of detecting subclinical lymphedema and early intervention, in order to reduce the affected limb's volume and prevent progression to a more advanced stage of BCRL.[18] Exercise therapy may be effective for patients with BCRL, and attention has been focused on the use of various compression garments during exercise,[19] although they cannot precisely control the compression pressure and there are several problems with their use. Therefore, as inappropriate lymphatic pressure increases can cause lymphatic failure,[8] it is necessary to scientifically define and accurately apply "appropriate compression" for patients with BCRL.

This clinical trial is designed to evaluate the efficacy of the Hand Incubator (Nippon Sigmax) for treating early-stage BCRL. This device is designed to apply uniform pressure and the operator can freely adjust the pressure. Therefore, the trial will evaluate the device's safety and efficacy during an exercise program that is completed under appropriate pressure, which will be selected based on the individual patient's lymphatic function. Each patient's baseline lymphatic function will be quantitatively assessed using ICG lymphography.

METHODS AND DESIGN

Study design

This multi-center rater-blinded study of early intervention with the Hand Incubator for BCRL (the BEAT-EDEMA trial) is registered in the UMIN Clinical Trials Registry (UMIN000026124). The study will use a two-arm randomized design and evaluate patients with stage 0–1 BCRL, based on the International Society of Lymphology criteria.[9] The study will be performed at the Nagoya University Hospital and Aichi Cancer Center Hospital (Aichi, Japan).

Patients will be provisionally registered before they undergo surgery for breast cancer, and will be definitively registered when they are diagnosed with stage 0–1 BCRL within 12 weeks after surgery. The participants will be randomized 1:1 into the intervention and control groups. All participants will individually complete upper limb exercises for 24 weeks, and the intervention group will complete grasping exercises in the Hand Incubator for 4 weeks. Measurements will be performed at baseline (before the intervention) and at 2 weeks, 4 weeks, 12 weeks, and 24 weeks after starting the intervention (Table 2). The effectiveness evaluations will be performed by blinded raters.

Ethical considerations

This study will be performed in compliance with the Declaration of Helsinki, the Pharmaceuticals and Medical Devices Act (PDM Act), and its enforcement regulations. The study's protocol has been approved by the Institutional Review Board of the Nagoya University Hospital (#282001).

Table 2 Treatment, examination, and observation schedule

		Informed consent	Screening	Provisional registration	Before surgery	Surgery	After surgery 4week	After surgery 8week	After surgery 12week	Definitive registration	Intervention start date: Before intervention	Intervention start date: After intervention	After starting intervention: 2week	After starting intervention: 4week	After starting intervention: 12week	After starting intervention: 24week
Upper limb exercise (intervention / control group)												→	→	→	→	→
Grasp exercise in Hand Incubator (intervention group)												→	→	→		
Vital signs, Body weight			●		●		●	●	●		●	●	●	●	●	●
Blood test			●								●			●	●	●
Urinalysis			●													
Urine pregnancy test			●				←	●	→							●
Effectiveness evaluation	Upper limb volume measurement				●						●	●	●	●	●	●
	L-Dex®				●		●	●	●			●	●	●	●	●
	ICG lymphography				●						●					●

Sample size calculation

Based on previous studies, a 50-mL decrease in upper limb volume (standard deviation: 37 mL) will be assumed to indicate efficacy.[18] Given a two-tailed significance level of 5% and a power of 80%, the required sample size is estimated to be 10 participants per group. To account for withdrawals, we will aim to definitively enroll 12 participants per group. In addition, based on an estimated incidence of 30% for lymphedema after breast cancer surgery, we aim to provisionally register 80 participants.

Potential participants

We will consider all patients who are undergoing surgery for breast cancer including axillary lymph node dissection within 24 weeks at the Nagoya University Hospital or Aichi Cancer Center Hospital.

Provisional registration

The eligibility criteria for provisional registration are patients undergoing surgery for breast cancer including axillary lymph node dissection within 24 weeks, age of >20 years, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1 (no limitations or light work is possible), ability to understand how to use the Hand Incubator, ability to keep an accurate diary, and providing written informed consent after receiving a sufficient explanation regarding the study's purpose, protocol, and expected risks.

The exclusion criteria are patients undergoing surgery for bilateral breast cancer or who have undergone surgery at the opposite breast; breast cancer stage 3–4; current or previous upper-extremity trauma with deformation, degenerative disease, or inflammatory disease; two or more concurrent diseases (cancers, collagen diseases, rheumatoid arthritis, nephrosis, heart failure, insect bites, cellulitis, or other edema); severely impaired circulation, congestive heart failure, or phlegmasia cerulea dolens; perceptual or sensory disorders at the Hand Incubator attachment site; inflammation, suppuration, painful skin diseases, or wounds at the Hand Incubator attachment site; hypersensitivity to vinyl chloride or polyurethane; allergies to ICG, iodine or hydrogel; an implanted pacemaker; pregnancy or lactation; the absence of written informed consent; and judged to be inappropriate for the study by the investigators.

After obtaining the participants' informed consent, data regarding their sex, date of birth,

height, smoking history, drinking history, dominant hand, ECOG PS, medical history, and medical complications will be recorded. The participants will also undergo screening tests to determine their blood pressure, pulse rate, body temperature, body weight, laboratory results, and pregnancy status. Patients who are provisionally registered will undergo preoperative testing of their upper limb volume, L-Dex® tests, and lymphatic function using ICG.

Definitive registration

Provisionally registered patients who are diagnosed with stage 0–1 BCRL using L-Dex® (an L-Dex® index increase of ≥10 compared to baseline) within 12 weeks after breast cancer surgery will be definitively registered in this study. The exclusion criteria for the definitive registration are the same as those for the provisional registration.

Informed consent

All participants will receive a sufficient document-based explanation regarding the study, and then their free written informed consent will be requested before the provisional registration. Participants will be able to withdraw from the study at any time without penalty.

Randomization

At the time of the definitive registration, an independent individual will perform the randomization using a computer-generated random number system. The patients and physicians will be aware of the group assignments, although the raters will be blinded to the assignments.

Exercise therapy

All participants will individually perform upper limb exercises using 0.5-kg dumbbells (or 500-mL polyethylene terephthalate bottles) according to a standardized program[20] for 24 weeks. In addition, the intervention group will perform 15-min grasping exercises in the Hand Incubator 3 times per day for the first 4 weeks. The Hand Incubator allows the user to place their hand inside the chamber and grasp under pressures of 20 mmHg, 30 mmHg, or 40 mmHg. The specific pressure for each participant will be determined using the lymph pressure value that is measured using ICG lymphography (Table 3).

Table 3 Lymphatic pressure measurement and Hand Incubator driving pressure setting

Lymphatic pressure measurement (by ICG lymphography)	Hand Incubator pressure setting
≤29 mmHg	20 mmHg
30–39 mmHg	30 mmHg
≥40 mmHg	40 mmHg

ICG: indocyanine green

Primary outcome measure

The primary outcome measure is the change in the volume of the affected upper limb after the Hand Incubator treatment (baseline vs. 24 weeks after the intervention), as measured using the water displacement method. The water displacement method is the most basic volumetric method, which exploits the fact that the volume of displaced water is equal to the volume of a submerged object.[21] After filling a container with water, the measured limb will be submerged

up to 10 cm proximal to the top of the olecranon, and the volume of the displaced water will be recorded. The volumetric measurements will be performed before the breast cancer surgery, before and after the intervention on the intervention start date, and at 2 weeks, 4 weeks, 12 weeks, and 24 weeks after starting the intervention.

Secondary outcomes measures

L-Dex® index

The L-Dex® device is a bioimpedance spectroscopy device that can diagnose unilateral lymphedema in the upper limbs. The L-Dex® index measurements will be performed before the breast cancer surgery; at 4 weeks, 8 weeks, and 12 weeks after the surgery; after the intervention on the intervention start date; and at 2 weeks, 4 weeks, 12 weeks, and 24 weeks after starting the intervention.

ICG lymphography

Lymphatic pressure measurements will be performed using ICG lymphography before the breast cancer surgery, before the intervention on the intervention start date, and 24 weeks after starting the intervention.

Other measurements

On the evaluation days, the participants' vital signs (blood pressure, pulse rate, and body temperature) and body weight will also be measured. Blood tests will be performed at the screening test, before the intervention on the intervention start date, and at 4 weeks, 12 weeks, and 24 weeks after starting the intervention. Urinalysis will only be performed at the screening test. Urine-based pregnancy tests will be performed at the screening test, during the 4–12-week period after surgery, and at 24 weeks after starting the intervention.

Data analysis

The primary outcome (change in upper limb volume) will be analyzed using the two-sample t-test. Lymphatic function (assessed using ICG lymphography) will be analyzed using Fisher's exact test, and changes in the L-Dex® index will be analyzed using the two-sample t-test. The significance level will be set at 5%.

DISCUSSION

There is currently no standard treatment for BCRL, although early intervention is thought to help slow or prevent the progression of BCRL. Therefore, if the findings indicate that exercise therapy using the Hand Incubator can prevent the progression of lymphedema, this approach may be useful for improving the postoperative quality of life among patients with breast cancer.

CONFLICTS OF INTEREST

This study is supported by the Japan Agency for Medical Research and Development (AMED). The authors have no other conflict of interest to disclose.

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