The effects of high-frequency moderate-intensity bicycling exercise in persons with lower limb lymphedema. A randomized controlled pilot trial.

Lower limb lymphedema

Lymphedema (LE) is a condition of increased interstitial fluid, caused by impairment in the lymphatic system. The impairment can be a result of congenital malformation of the lymphatic system but is much more common after cancer treatment, being a well-known side-effect (1). LE is considered to be a chronic condition with a negative impact on quality of life (2-4), physical activity, as well as social activities (3). The incidence of lower limb lymphedema (LLL) secondary to treatment for malignant melanoma or gynecological cancer increase after more extensive lymph node dissection (5-7) and radiation therapy (8-12). After treatment for malignant melanoma the incidence of LLL varies from 14% to 34% (5,8,12) and after gynecological cancer treatment from 13% to 37% (7,9,11). The diversity in the numbers reported is due to the lack of consensus of standardized assessment of LLL (13).

Treatment

After the initial management of LLL consisting of decreasing the swelling, and education in important parts of the self-management (i.e. skin care, exercise/ movement and elevation, weight control and self-monitoring) compression garments play an important role in limiting further deterioration (1). The compression garments should be replaced regularly to secure continuous treatment and thus maintain a stable swelling (1) since no curative treatment of LE exist.

Exercise

Exercise interventions is of main importance in cancer rehabilitation since it has been shown that higher levels of physical activity are associated with improved survival in many cancer diagnosis (14-16). The prescription of exercise should be based on general principles such as moderate intensity for at least 150 minutes per week combined with resistance training twice a week (17). Previously it was assumed that moderate and vigorous exercise may overload the lymphatic system and consequently, many patients were advised to be careful. However, nowadays it has been proven that progressive regular exercise is safe and does not worsen the LE, at least for those with upper limb LE (18).

For those with LLL, the effects of moderate or vigorous exercise have been investigated in only a few studies evaluating water exercise (19-21), bicycling exercise (22) and land exercise (23). None of the studies reported any adverse effects on the LE limb after the intervention compared to before. On the contrary, in some of the studies (20, 22, 23) there was a decrease in total limb volume in the

exercise group as well as in the control group after intervention compared to before. The decrease in the control group could be because this group also had some kind of active lymphedema treatment (20, 22, 23). Lindquist et al (19) concluded that there were too few participants with LLL to draw any conclusions about the effects of exercise on the lower limbs, while Dionne et al (21) found significant improvements in the LE postintervention compared to preintervention in their small sample study.

Comparing the frequency of exercise performed in these studies a large variation was revealed. In the study by Fukushima et al (22), the exercise was performed only at two occasions. Lindquist et al (19) examined once a week exercise for 10 weeks, while twice a week exercise for 6 weeks was investigated by Dionne et al (21) as well as Ergin et al (20), and five times a week exercise for four weeks in the study by Do et al (23). Thus, there is lacking knowledge about the impact of high frequency exercise on the LLL.

The rationale for this intervention study is therefore to evaluate if high frequency bicycling exercise at a moderate intensity is feasible and effective to increase physical fitness and quality of life without deteriorating LL volume, extracellular fluid and local tissue water in persons with LLL.

The objective

The main objective of this study is to evaluate the feasibility and effects of high frequency moderate bicycling exercise for 8 weeks in persons with LLL. Primary outcomes are changes in volume, local tissue water and arm-to-leg impedance in the lower limbs. Secondary outcomes are effects on cardiovascular fitness, health-related quality of life, subjective assessments of function, heaviness and tightness in the lower limbs.

Our hypothesis is that high-frequency bicycling exercise on a moderate intensity is feasible, and that the intervention can increase fitness and health-related quality of life without worsening the LE.

Method

The study design is a randomized control trial (RCT) with an allocation ratio of 2:1 (for the exercise group vs. control group). The allocation ratio was chosen due the limited number of suitable participants and the assumption that a higher opportunity to be randomized to exercise group would attract participants to enroll. A total number of 30 participants is considered enough since this is a feasibility study and no preliminary data are available. The participants will be identified at physical therapy units or rehabilitation units in the Southern Health Care Region of Sweden and eligible criteria are:

1. Uni- or bilateral, primary or secondary LLL
2. Persistent lymphedema for at least 6 months
3. A volume variation of less than 5% for each limb during the last 6 months

Exclusion criteria are: i) recurrence of the cancer; ii) language limitations or dementia; iii) presence of concurrent diseases or medication affecting the limb volume or inability to perform bicycling exercise.

When the diagnosis of LLL is not secondary to cancer treatment the diagnosis must be verified by lymphoscintigraphy. For secondary unilateral LE, the LE is defined as an interlimb discrepancy of 5% or more (24) and the presence of palpated increased skin and subcutaneous tissue thickness (25) on the calf and/ or thigh of the affected limb comparing to the non-affected limb. For bilateral LE, a palpated increased skin and subcutaneous tissue thickness (25) on the calf and/ or thigh of the more affected limb and on the less affected limb have to be present.

To maintain a steady LL volume before the 8-week study, compression garments should be worn daily, or day and night, according to usual care. At the start of the study, the compression garments should not be older than two months. If new ones are needed the same size should be ordered, and the new garments should be used for at least two weeks before inclusion in the study. At least two sets of garments should be provided.

Oral and written information about the study and enrollment of participants will be performed by one physiotherapist (CJ). After written informed consent all assessments will be performed starting with the subjective assessments, followed by assessments of lymphedema status and fitness. At last assignment to either exercise or control group will be performed. The random allocation sequence will be done using a computer software program generating the random sequence administered by one of the supervisors (KJ). After the intervention another physiotherapist (AJ), blinded to participant group status, will perform all the assessments except circumference measurements along the limb and markings for the assessments of local tissue water which will be performed by the physiotherapist CJ. The participants will be asked not to discuss their group assignment with the physiotherapist AJ.

Intervention

The exercise group

The exercise group will perform moderate bicycling exercise on their own, on a private bicycle either outdoors or indoor, or on an indoor spinning bike provided by us or at a gym (if the participant has access to a gym). The exercise should be performed 3 to 5 times a week for 8 weeks with a mean intensity of 40 - 59% of the Heart Rate Reserve (the maximum heart rate minus the resting heart rate) (17). Each session should last 30 to 60 minutes, corresponding to a perceived exertion rate of 12-14 on Borg scale (”somewhat” hard) (26). Polar FS 1 heart rate monitor, provided by us, will be used to monitor the heart rate. Prior to each exercise session there will be some warming up exercises consisting of biking at a self-chosen speed for 5 minutes. After each session there will be a cool down period consisting of biking at a self-chosen pace and stretching. Written and verbally instructions about the exercise sessions, the Polar heart rate monitor, the Borg scale, the warming up, cooling down and stretching will be provided at baseline measurements.
A logbook will be used to register; i) date for each exercise session; ii) the subjective sensation of heaviness and tightness in the lower limbs on a Visual Analog Scale, prior to each exercise session and after; iii) total time for the exercise session in minutes; iv) average heart rate during the exercise session; v) any adverse events related to the performance of the exercise. The logbook will be checked every two weeks during the intervention together with the assessments of LL volume by CJ.

The control group

The participants will be encouraged to maintain their usual daily routine during the 8 week-period. If they are involved in any form of physical activity or exercise, regular or more spontaneously they will be allowed to continue with such activities.

Measurements

The measurements for primary outcomes are: i) LL volume; ii) local tissue water; iii) arm-to-leg impedance. The measurements for secondary outcomes are; i) cardiovascular fitness; ii) the health-related quality of life questionnaire (Lymphedema quality of life Inventory, LyQLI); iii) the function, disability and health questionnaire for LLL (Lymph-ICF-LL) and iv) perception of heaviness and tightness in the LE limb/ limbs. A questionnaire reporting leisure time physical activity during the last 6 months will be used to describe the physical activity status. At the end of the study some questions regarding exercise during the intervention will be answered. The purpose of these questions is to clarify the degree of exercise in addition to bicycle exercise in the exercise group and in the control group. Feasibility will be assessed using retention to exercise or control group and adherence to the exercise. Any adverse events will be reported.

Lymphedema measurements

All the measurements will be taken after removal of the compression garments and resting for about 10 minutes in a supine position. Before the start of the measurements a 110 cm measuring board will be placed under the limb to measure.

Lower limb volume for each limb will be assessed using the tape measurement method based on circumference measurements every 4 cm along the limb starting at the ankle 10 cm above the heel and ending near the groin. Total limb volume will be calculated applying the truncated cone formula (27) calculated in an excel-file (Brorson, Dept of Plastic and Reconstructive Surgery, Skåne University hospital). The tape measurement method has shown high reliability in persons with LLL (28).

Local tissue water will be assessed at 14 different points on the calf and the thigh described in a previous study (28) using the device MoistureMeterD (Delfin Technologies Ltd, Finland). With the use of high frequency electromagnetic wave, a tissue dielectric content (TDC) directly proportional to tissue water content in the skin will be calculated (29). Measurements will be repeated at each point until two values differ less than 1.0 units and a mean value of those two will be used. The reliability, of the TDC method in the 14 different points has shown to be fair to excellent in persons with LLL (28).

Arm-to-leg impedance will be calculated assessing the impedance to extracellular fluid by bioimpedance spectroscopy (BIS), in the upper and lower limbs using a SEAC SFB7 monitor (SEAC Australia, Impedimed). BIS assess the electrical resistance (impedance) at different frequencies. Arm-to-leg ratio as a measure of extracellular water, will be calculated using the formula of dominant arm R_0/ dominant leg R_0 and nondominant arm R_0/ nondominant leg R_0, respectively and a percentage change over time for R_0 is reported to range from 14.0% to 14.7% (30).

Fitness, health-related quality of life, subjective assessments of function and perceptions of LE

Cardiovascular fitness will be assessed using a sub-maximal bicycle ergometer test (31) and estimation of maximal oxygen uptake from heart rate and workload (VO_{2max}) will be evaluated. During the cycling test the heart rate and the cadence will be monitored every minute together with the person's perceived exertion using the Borg RPE-scale (26). The cadence will be 50 revolutions per minute until "steady-state" will be reached. The perceived exertion rating on the Borg scale should be "somewhat hard" (12-14), corresponding to a moderate intensity. For safety reasons, the test will be interrupted if the perceived exertion is rated more than 15 on Borg RPE-scale or the

heart rate exceed 150 beats per minute (31). The test-retest reliability expressed as CV has shown to be 9.8% (32).

The disease-specific, health-related quality of life questionnaire; Lymphedema Quality of Life Inventory (LyQLI) will be used. It contains 45 items in the three domains: physical, psychosocial and practical, and has shown good validity and reliability (33) and responsiveness (34) and a Swedish version is available.

The function, disability and health questionnaire for LLL (Lymph-ICF-LL) will be used. It contains 28 questions about impairments in function, activity limitations, and participation restrictions divided in 5 domains: physical function, mental function, general tasks/ household activities, mobility activities and life domains/ social life. The questionnaire has shown good validity and reliability (35) and a Swedish version is available.

The perception of heaviness and tightness in the LE limb/ limbs, during the last week, will be assessed using a 100-millimeter Visual Analogue Scale (VAS) with the endpoints "no discomfort" (0 mm) and "worst imaginable" (100 mm) (36). This scale has been used in prior studies to measure the perception of heaviness and tightness in lymphedema arms (37-39).

Physical activity status will be assessed by a questionnaire (40) to determine leisure time physical activity during the last 6 months.

Feasibility

Feasibility will be evaluated using retention during the intervention and adherence will be assessed using the information from the logbook such as number of exercise sessions performed and time for each session. The participants will be encouraged to take notes in the logbook about the experience of the training and of any adverse events related to the performance of the exercise.

Statistical methods

Independent sample t-test and Mann-Whitney U test are used for evaluating differences between the groups. Paired sample t-test and Wilcoxon are used for evaluating changes within each group. A p value of<0.05 will be considered statistically significant.

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