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RESEARCH

Effects of an early intervention with Hyperbaric Oxygen Treatment on arm lymphedema and quality of life after breast cancer—an explorative clinical trial

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Abstract

Purpose Lymphedema (LE) is a common complication after breast cancer treatment, which negatively affects the quality of life (QOL). Hyperbaric Oxygen Treatment (HBOT) is an established treatment for radiation-induced tissue injury, but evidence of effect on breast cancer-related LE is inconclusive. We aimed to explore effects of HBOT on early breast cancer-related LE and the implications for QOL.

Methods We invited women with breast cancer treated with surgery, axillary dissection and radiotherapy, who had participated in a randomized controlled trial and who presented with LE 1 year after surgery. In a prospective observational study design, change in LE was assessed with perometry, dual-energy X-ray absorptiometry (DXA) and lymphoscintigraphy, and QOL by validated self-report scales. Participants were offered 40 sessions of HBOT on every weekday for 8 weeks and were followed for 6 months.

Results Out of 50 eligible participants, 20 women accepted participation. Nineteen women initiated and completed treatment and follow-up. None of the objective measures of LE severity showed consistent changes during the study period, but participants reported significant improvements in QOL (physical functioning, fatigue, insomnia and breast and arm symptoms), with improvements peaking at 6-month follow-up.

Conclusion Participants receiving HBOT experienced improved QOL without consistently significant changes in arm mass, volume or lymphatic drainage. These results call for studies into differential effect in patient sub-groups, and a large-scale, randomized placebo-controlled trial with long-term follow-up to assess the effect of HBOT in patients with soft tissue radiation injuries after breast cancer seems warranted.

Trial registration Danish Health and Medicines Authority, EUDRACT no. 2015–000,604-25 Ethical committee of the Capitol Region, No. R96-A6604-14-S22.

Keywords Breast neoplasms · Lymphedema · Hyperbaric oxygen therapy · Health-related quality of life · Soft tissue radiation injury

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Introduction

Patients with breast cancer (BC) may undergo a treatment combination of surgery involving axillary lymph node dissection (ALND), radiotherapy, and systemic chemotherapy. All three treatments increase the risk of lymphedema (LE) development [1, 2] which affects up to 60% of survivors [3]. The negative consequences for quality of life (QOL) and physical function are well established [2, 4–6]. To date, there is no effective cure for LE [7], and patients are dependent on compression garments and specialist treatments for containing the symptoms and maintaining physical function [8, 9]. Patients with LE may also experience a number of additional treatment side effects, such as pain, shoulder dysfunction, skin fibrosis and sometimes necrosis. Furthermore, problems with cognition, fatigue, physical function and psychological wellbeing constitute a substantial burden which leads to reduced QOL [10, 11]. Limiting the impact of treatment side effects has paramount importance due to the increasing population of long-term BC survivors.

LE is characterized by the accumulation of extracellular fluid in the affected body area. When filtration of lymph into the interstitial space exceeds the ability of the lymphatic system to drain the lymph back into the blood stream, it results in progressive swelling and chronic tissue inflammation. In long-standing LE, the accumulated fluid leads to the formation of fatty fibrotic tissue, at which point the LE may be considered irreversible [8]. The strongest treatment-related risk factors are ALND, radiotherapy and taxane-based chemotherapy, whereas modifiable risk factors include obesity and physical inactivity [12].

Hyperbaric Oxygen Treatment (HBOT) may be used for the treatment of pelvic radiation-induced tissue injury such as osteonecrosis, skin necrosis, haemorrhagic cystitis or proctitis [13–16]. Further, a prospective study showed improvements in, e.g. pain, swelling and hypersensitivity in patients participating in HBOT ($n = 57$) [17]. The few previous studies examining the effect of HBOT on BC-related LE have shown an overall poor treatment potential with respect to changes in LE arm volume, possibly due to inclusion of patients with chronic and thus irreversible changes caused by LE and small sample sizes [18–21]. However, when considering the physiological effects that HBOT initiates, such as neovascularization, re-organization and reduction of fibrous tissue as well as an increase in the number of lymphatic vessels in the sub-epithelial irradiated area [22, 23], it is possible that HBOT can reduce LE in the early stages where tissue changes have not yet become irreversible. Furthermore, HBOT has been shown to improve QOL in patients treated with radiotherapy and chemotherapy [24]. This calls for an explorative trial using objective LE measurements in combination with patient-reported symptoms and QOL to investigate the effect of HBOT from different perspectives [17, 21, 25].

Accordingly, this study aimed to examine if an early intervention with HBOT could reduce the extent of arm volume and improve lymphatic drainage along with improving overall QOL in women with BC-related LE who had received ALND and radiotherapy 1 year prior to HBOT intervention.

Methods

Study design and population

The present study is an explorative one arm clinical trial. Participants were recruited from LYCA, a multi-centre RCT that examined the effect of progressive resistance training in women with primary unilateral BC who had undergone surgery with ALND followed by radiotherapy [26, 27]. Eligibility for participation in the current explorative trial was determined by the presence of clinically relevant LE at LYCA study end. We used the same definitions of LE as in the original multi-centre RCT and defined clinical relevance by > 2 points for swelling/heaviness/tightness on Numeric Rating Scale (NRS), manifestation of swelling in clinical examination (pitting, skin thickness, bony landmarks and visibility of veins), and finally $\geq 3\%$ increase in interlimb volume difference between the affected versus the unaffected arm from 2 weeks post-surgery to 1-year follow-up [28–31].

Upon final LYCA assessment and confirmation that clinically relevant lymphedema was present, patients were informed verbally and in written about the HBOT trial. All consenting patients were checked for contraindications (pregnancy, undrained pneumothorax, inability to equalize ear pressure in spite of drain treatment, untreated severe heart failure and claustrophobia not resolvable using mild anxiolytics). The HBOT treatment regime consisted of 40 days of pressure exposures performed on every weekday for 8 weeks in a multi-place hyperbaric chamber at Rigshospitalet. One treatment session consisted of a 5-min compression period, followed by 90 min at 2.4 atmosphere absolute (ATA) and finally a 5-min decompression period. Oxygen breathing was administered by means of a transparent o-ring sealed hood (model Amron®) ensuring spontaneous breathing with 100% oxygen (inspiratory oxygen fraction = 1.0).

The study was approved by the Danish Health and Medicines Authority, EUDRACT no. 2015–000,604-25, and the ethical committee of the Capitol Region, No.

R96-A6604-14-S22, and was monitored by an independent unit for Good Clinical Practice [32].

Measurements

Figure 1 shows the timeline for treatment and measurements in the study period.

Dual-energy X-ray scans (DXA) were performed and the % Inter Limb Soft Tissue Mass Difference (% ILMD) was calculated as the difference between limbs relative to the unaffected arm. The accuracy of DXA to detect changes in the affected arm total volume has been reported to be 1.2% [33]. DXA measurements were carried out with a Lunar iDXA scanner (ME + 210,770) (Madison, WI, USA) using Encore software version 16 and the small animal software (medium 2–20 kg) as described by Gjørup et al. [34, 35].

Quantitative lymphoscintigraphy assessed lymph transport by injecting a technetium-99 m labelled radiopharmaceutical (Nanocoll, GE Healthcare, IT) into the digital fossa between the second and third fingers on the dorsum of both hands. Lymphoscintigraphy has been found to have high sensitivity (96%) and specificity (100%) ({Hassanein, 2017 #837}REF). Planar images were taken at $t = 0$ h and $t = 2$ h using a dual-head gamma camera. In an attempt to find the most appropriate procedure for the quantitative lymphoscintigraphy measurements, we included a resistance exercise session between $t = 0$ and $t = 2$ h for the first 9 participants and usual care (allowed to walk around but not leave the premises) for the remaining 10 participants. All patients were instructed to limit the intake of diuretic fluids and avoid using compression garments on the same day prior to the measurements. Lymph transport was measured as the decrease in activity in the identical *Regions of Interest* of the hands. The images at $t = 2$ h assessed whether the affected arm had diffuse activity (i.e. organised lymphedema) or axillary lymph node concentrated activity (i.e. normal).

Perometry assessed limb volume using the Perometer 400 T (Pero-system Messgeräte GmbH, Germany), which is an optoelectronic volume approximation method, where infrared light blocked by the limb allows a software algorithm to estimate the surface area of the arm [36]. Measurements were taken on the affected arm and recorded in millilitres. Due to lack of coordination of measurements taken by different hospital departments, we were not able to present inter-limb volume measurements by perometry. The positioning of the patient was standardized with the patient sitting on an adjustable chair holding onto a standard block-weight positioned within a marked area.

We used validated scales for the assessment of symptoms and QOL.

Lymph-ICF (upper limb module) scale was used to assess the functional limitations in patients with LE, and scores reflect a percentage of the maximum score for the subscales of physical function, mental function, housework, mobility and movement, social function and a total for all subscales collectively [37]. A higher score reflects worse function.

Health-related QOL was assessed using the European Organization for Research and Treatment in Cancer (EORTC) core scale (C30) and BC specific scale (BR23) [38, 39]. Scores are given as a percentage of maximum and for function subscales higher score is better whereas for symptom subscales higher score is worse.

Anxiety and depression were assessed using the Symptom Check List-92 [40] and Major Depression Inventory [41, 42], respectively. A higher score represents worse mental health.

Fatigue was assessed with the validated Functional Assessment of Chronic Illness Therapy—fatigue scale (FACIT-f) [43], which is a 13-item stand-alone scale where the maximum score is 52, and the higher the score, the lower the level of fatigue.

Pain was assessed using a content-validated questionnaire [44] including specific questions regarding the affected area (breast area, side of the thorax, axilla or arm on the operated side), pain intensity reported on NRS (0 = no pain, 10 = worst pain), and we classified participants as having pain if it was experienced on a weekly basis as a minimum.

The NeuroPathic Pain Score (NeuPPS) has been designed to specifically capture neuropathic pain in postsurgical patients and has been Rasch-validated [45]. Participants were asked to report symptoms for the last week, in terms of (i) pins and needles, tingling or stabbing sensations; (ii) electrical shock or jolt; (iii) heat or burning sensation; (iv) hypersensitivity to clothes or touch; and (v) cold-provoked

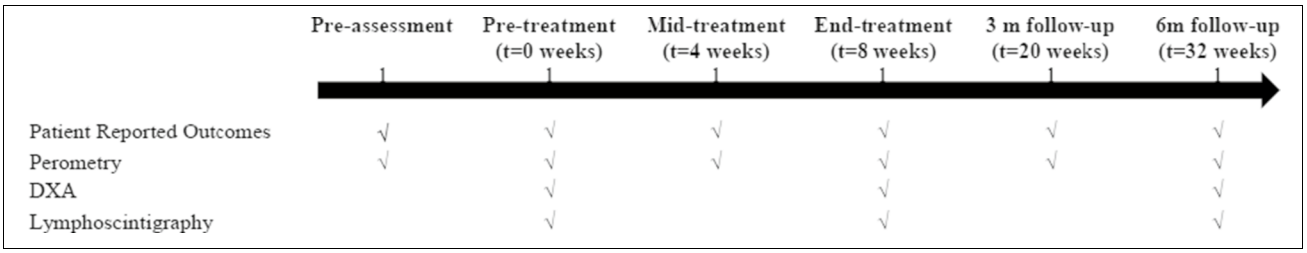

Fig. 1 Timeline and measurements in the LYCA-HBOT study, Copenhagen, 2018–2020

pain. Each symptom gave one point, adding up to a NeuPPS score ranging from 0 to 5 [45].

Adverse events and side effects to the HBOT intervention were recorded after every treatment session throughout the course of the HBOT treatment and at 3- and 6-month follow-ups.

Data analyses

Participants' characteristics were presented as means with standard deviations (SD) for demographic and clinical information. Change in outcomes over time was assessed by univariate mixed effects models for repeated measurements for each outcome, presented as mean values and SD for each measurement time point, and estimates for β with 95% confidence intervals (CI) and *p*-values. Sensitivity analyses (stratified box plots and adjusted models) assessed if the lymphoscintigraphy procedure with/without strength training and whether belonging to intervention or control in the LYCA study had affected the results. In post hoc analyses, we assessed if there was an effect modification for baseline ILMD ($\leq 10, > 10\%$), BMI ($\leq 30, > 30$ kg/m^2) and number of positive lymph nodes ($\leq 1, > 1$), by adding interaction terms in the models. With the small sample size and great biological variation between participants, we explored various Δ-measurements for physical outcomes such as absolute change, change in the affected arm relative to the non-affected arm and a change ratio between the affected and non-affected arm. All statistical analyses were discussed with a senior statistician and performed by GA in STATA, v. 14.2.

Results

Out of the 158 LYCA participants, 130 were evaluated for LE at 1-year follow-up, and 50 were eligible for this trial. Twenty participants accepted participation and one withdrew consent prior to treatment commencement, leaving 19 participants in the trial, all completing treatment and follow-up.

Participant demographics and clinical information can be seen in Table 1. Participants were middle-aged, with above-average BMI and 7 participants were obese. The mean weight change of the participants was 1.5 kg in the study period (standard deviation 3.5 (min. − 8.5 kg and max. 5.8 kg)). The majority of participants had lumpectomy and the mean number of lymph nodes removed in ALND was 19. Neo-adjuvant chemotherapy including taxanes had been administered to 7 participants, and adjuvant chemotherapy to 10, whereas all participants received radiotherapy. Twelve participants had been allocated to the progressive resistance training arm in the LYCA trial. Most participants were physically active more than 30 min per day. One participant was a current smoker despite advice that HBOT works better for non-smokers.

Physical outcomes

We found no consistent significant differences in ILMD as measured by DXA, but a tendency towards an increase when looking at the arm as a whole and lower arm isolated at the end of HBOT treatment. Conversely, with regard to lymphatic drainage assessed by lymphoscintigraphy and limb volume by perometry, the tendency was non-significantly reduced volume and improved drainage (Tables 2 and 3). Sensitivity analyses showed no different patterns of effect in physical outcomes for intervention or control participants in the LYCA RCT, nor between obese versus non-obese participants, ≤ 1 versus > 1 positive lymph nodes removed, or baseline ILMD ≤ 10 versus > 10 (data not shown). We noted that physical measurements had a wide range both in the normal and the affected arms.

Patient-reported outcomes

The self-reported functional ability measured by Lymph-ICF improved significantly with time in the study (Table 4), with an 8% (CI − 14.84; − 0.87) lower total score at 6-month follow-up. The change in the total score was driven primarily by the physical function subscale with a 12-point (CI − 19; − 5) improvement found at 6-month follow-up. Further, for the mobility/movement subscale, a borderline significant 7-point (CI − 15; 0) reduction was found at 6-month follow-up.

Results of selected relevant subscales in the EORTC C30 and BR23 modules are presented in Table 5. For the fatigue subscale, we found a significant overall trend for improvement over time ($p < 0.001$), although the change from baseline to 6-month follow-up was non-significant ($\beta = -16$, CI –33; 1). Patients experienced significantly less insomnia at 6-month follow-up with a 12-point improvement from baseline (CI − 29; − 2). For the breast symptoms subscale, there was a 9-point improvement from baseline to 6-month follow-up (CI − 17; − 2).

Results of analyses on pain, symptoms of swelling and fatigue are presented in Table 6. Participants experienced only mild pain in the study period (< 3 points on a 0–10-point scale). For intensity of worst pain in the previous 24 h, we found a statistically significant 1.3-point reduction (CI − 2.4; − 0.2) from baseline to 6-month follow-up. For neuropathic pain, we found a significant trend of reduced symptoms with time in the study ($p < 0.001$), although the estimates for each measurement time point were non-significant. Lymphedema symptoms (heaviness, swelling and tightness) were significantly reduced,

Table 1 Sociodemographic, clinical and lifestyle information for 19 participants in the LYCA-HBOT study, Copenhagen, 2018–2020

Variable		Mean/*n*	Sd/%
Age, years		53.9	9
Cohabitation, *n*	Living with partner	13	68
	Living alone	6	32
Highest attained education, *n*	General/technical (< 12 years)	7	37
	Short-cycle higher (12–14 years)	4	21
	Medium-long cycle higher (> 14 years)	8	42
Employment, *n*	Employed full- or part-time	4	21
	Unemployed or not in work-market	14	74
	Data missing	1	5
BMI, kg/m^2		29.4	5
BMI categories, *n*	> 20 to ≤ 25 kg/m^2	5	26
	> 25 to ≤ 30 kg/m^2	7	37
	> 30 to ≤ 35 kg/m2	4	21
	> 35 to ≤ 40 kg/m2	2	11
	> 40	1	5
Duration of LE symptoms* Months, mean (min, max)		8.5 [2, 15]	
Histological stage, *n*	1	1	5
	2	7	37
	3	6	32
	Data missing	5	26
Type of surgery, *n*	Lumpectomy	11	58
	Mastectomy	8	42
Lymph nodes, mean	No. removed	19	9
	No. positive	1.8	2
Tumour diameter, mm		20	9
Chemotherapy, *n*	Adjuvant	10	53
	Neo-adjuvant	7	37
	No chemotherapy	2	11
Hormone treatment, *n*	Yes	14	74
	Data missing	5	26
Receptor status, *n*	Estrogen receptor-positive	16	84
	HER2 positive	7	37
Physical activity, *n*	0 < 30 min./day	1	5
	≥ 30 min./day	7	37
	≥ 30 min./day + high int. > 2 × week	10	53
	Data missing	1	5
Smoking, *n*	Current smoker	1	5
	Ex-smoker	10	53
	Never smoker	8	42
Alcohol consumption	No. of units per week, mean	4.4	5.4
	No alcohol consumption, *n*	5	26
	Data missing, *n*	2	11

BMI, body mass index; *HER2*, human epidermal growth factor receptor 2. All participants had undergone axillary lymph node dissection and received radiotherapy to the axilla. *Self-reported duration of symptoms at time of inclusion

and at 6-month follow-up there was a 2-point reduction (CI − 3; − 1). Patient-reported fatigue improved significantly at each measurement time point with the largest improvement seen at 6-month follow-up (− 24 points, CI − 33; − 15).

Results for the remaining subscales of the Lymph-ICF, EORTC C30 and BR23 as well as scales for depression and anxiety are shown in Online Resources 1, 2 and 3. We found that emotional functioning had improved significantly with an 11-point increase at 6-month follow-up (CI 3; 19). For

Table 2 Absolute and delta values for physical measurements of arm lymphedema through the intervention period and 6 months' follow-up for 19 women in Hyperbaric Oxygen Treatment initiated 1 year after breast cancer surgery with axillary lymph node dissection followed by radiotherapy. The LYCA-HBOT study, Copenhagen, 2018–2020

Measurement description		Time-point or Δ period (Median (IQR)		
Absolute measurements		Baseline	End-HBOT	6 months' follow-up
DXA soft tissue mass (g)	Affected arm	2967 (629)	3041 (572)	2943 (563)
	Non-affected arm	2884 (536)	2906 (620)	2981 (645)
Lymphoscintigraphy Clearance (%)	Affected arm	9.9 (6.1)	9.5 (5.7)	12.5 (4.6)
	Non-affected arm	12.3 (6.3)	11.4 (5.9)	14.7 (5.9)
Perometry volume (ml)	Affected arm	5420 (964)	5440 (744)	5240 (657)
DXA, soft tissue mass (g)		**Absolute Δ**	**Δ affected arm in % of non-affected arm**	**Δ affected arm/Δ non-affected arm**
Δ Baseline to end-HBOT	Affected arm	73 (274)	2.7 (8.7)	47 (207)
	Non-affected arm	22 (267)		
Δ End-HBOT to 6 months' follow-up	Affected arm	−97 (151)	−3.3 (4.6)	0.3 (3)
	Non-affected arm	74 (221)		
Δ Baseline to 6 months' follow-up	Affected arm	−24 (224)	−0.7 (7.4)	−0.5 (2)
	Non-affected arm	96 (320)		
Lympho-scintigraphy clearance (%)		**Absolute Δ**	**Δ affected arm in % of non-affected arm**	**Δ affected arm / Δ non-affected arm**
Δ Baseline to end-HBOT	Affected arm	9.9 (6.1)	6.6 (61.8)	0.4 (1.7)
	Non-affected arm	12.3 (6.3)		
Δ End-HBOT to 6 months' follow-up	Affected arm	−0.4 (5.6)	34.8 (60.5)	0.0 (1.9)
	Non-affected arm	−0.9 (6.8)		
Δ Baseline to 6 months' follow-up	Affected arm	3 (5.6)	34.0 (57.9)	0.3 (0.9)
	Non-affected arm	3.4 (6.6)		
Perometry (ml)		**Absolute Δ**		
Δ Baseline to end-HBOT	Affected arm	52 (912)	-	-
Δ End-HBOT to 6 months' follow-up	Affected arm	−200 (721)	-	-
Δ Baseline to 6 months' follow-up	Affected arm	−261 (805)	-	-

DXA, dual-energy X-ray absorptiometry; *HBOT*, Hyperbaric Oxygen Treatment

Absolute Δ: absolute change in the specified period

Δ affected arm in % of non-affected arm: change in the specified period for the affected arm given as a percentage of the non-affected arm

Δ affected arm/Δ non-affected arm: change in the specified period for the affected arm divided by change in the specified period for the non-affected arm

- not calculated due to no contralateral measurement

the other subscales (global health; physical, role, cognitive and social functioning; nausea; pain; dyspnoea; constipation; diarrhoea; financial worry; body image; sexual function; worry about future perspective; systemic and arm symptoms), there was no significant change.

Adverse events

Complications were confined to single occasions of problems with equalizing pressure in the ears ($n=2$). Whereas one resolved with nose drops and spontaneously recovered, the other was resolved with ear drum puncture by ear and nose specialist, which resulted in temporary reduced hearing. Myopia was reported by 1 person, which resolved spontaneously. One participant experienced breast cancer recurrence during the follow-up period, an incidence classified as unlikely related to HBOT.

Discussion

In this explorative one-arm clinical trial, 19 women with LE after breast cancer underwent a HBOT programme. Participants experienced improvements in self-reported QOL with regard to physical functioning, fatigue, insomnia and breast and arm symptoms both during treatment, and interestingly, the effects peaked at 6 months after end of HBOT treatment. None of the physical examinations of LE (arm mass, lymph drainage or arm volume) demonstrated consistent significant changes during the observation period.

Table 3 Physical measurements and change in arm lymphedema through the intervention period and 6 months' follow-up for 19 women in Hyperbaric Oxygen Treatment initiated 1 year after breast cancer surgery with axillary lymph node dissection followed by radiotherapy. The LYCA-HBOT study, Copenhagen, 2018–2020

Outcome		Time	Mean (sd)	β	95% CI	P
DXA (interlimb % difference in soft tissue mass)	Whole arm	BSL	6.2 (7.5)			
		End HBOT	8.3 (8.6)	2.1	0.4; 3.8	0.02
		6 m FU	8.5 (8.6)	2.3	−0.2; 4.8	0.07
		Overall				0.034
	Upper arm	BSL	7.3 (10.0)			
		End HBOT	8.8 (11.3)	1.5	−0.6; 3.5	0.16
		6 m FU	9.4 (12.5)	2.1	−0.6; 4.7	0.12
		Overall				0.192
	Lower arm	BSL	5.5 (9.7)			
		End HBOT	9.2 (11.1)	3.7	0.3; 7.0	0.03
		6 m FU	8.8 (10.1)	3.3	−1.4; 8.0	0.15
		Overall				0.063
	Hand	BSL	2.3 (7.3)			
		End HBOT	4.7 (9.2	2.3	−1.7; 6.4	0.24
		6 m FU	3.4 (5.5)	1.1	−1.0; 3.1	0.30
		Overall				0.362
Lymphoscintigraphy* (interlimb % difference in lymphatic clearance)		BSL	−17.7 (44.7)			
		End HBOT	−8.2 (59.7)	9.5	−24.6; 43.5	0.57
		6 m FU	−9.7 (30.7)	8.0	−13.5; 29.6	0.44
		Overall				0.711
Perometry (affected arm, ml)		Pre HBOT	5495 (817)			
		BSL	5420 (964)	−188	−726; 349	0.47
		Mid HBOT	5389 (732)	−205	−686; 276	0.38
		End HBOT	5440 (744)	−153	−664; 358	0.54
		3 m FU	5302 (674)	−292	−693; 109	0.14
		6 m FU	5240 (657)	−353	−794; 87	0.11
		Overall				0.422

All analyses are unadjusted. *Lymphoscintigraphy analysis was adjusted for performing resistance training during test procedure. Time Pre HBOT = Pre-treatment examination; BSL = pre-treatment day 1 of Hyperbaric Oxygen Therapy (HBOT); Mid HBOT = pre-treatment day 20 HBOT; End HBOT = post treatment day 40 HBOT; 3 m FU = 3 months follow-up after end HBOT; 6 m FU = 6-month follow-up after end HBOT. Overall = effect of time in the study. *DXA*, dual-energy X-ray analyses. Figures in bold: p-value < 0.05. *SD*, standard deviation; *B*, units change from baseline; *CI*, confidence interval

Earlier studies have examined the effects of HBOT on breast cancer-related LE [17–21, 46] with mixed results. The studies were conducted on populations with a short follow-up time, and time from treatment ranged from 1 to 27 years and therefore included patients with often longstanding changes of LE. It has been argued that the lack of consistent results could be attributed to the pathophysiological changes of long standing LE and the limited possibility for fibrotic tissue to remodel [18]. In this study, we had the possibility to recruit patients at 1 year post diagnosis, and therefore their LE history was limited to maximum 1 year.

In our study, patient-reported outcomes were improved, whereas the physical examinations of LE were largely unchanged (Table 2). This is in line with previous reports for patients with long-term LE, where similar methods for physical evaluation of LE showed no difference between intervention and control [18] or were not performed [17, 21]. Interestingly, improvements in patient reported outcomes were found in two observational studies [17, 21]. The first study examined effect on long-standing LE ($n = 32$) and compared with 12 controls, and found that participating in 25 sessions of HBOT caused improvements in self-reported pain, oedema and erythema in the long-term follow-up [21]. In the other study ($n = 57$) participating in 47 sessions of HBOT was associated with significant improvements in pain, swelling, shoulder movement and breast symtpoms [17].

Further, a small pilot RCT ($n = 10$) found that participating in 10 sessions of HBOT plus Complete Decongestive Therapy was better than Complete Decongestive Therapy alone and caused benefits on self-reported physical function while no

Table 4 Change in patients' self-reported lymphedema-related quality of life by the Lymph-ICF scale through the intervention period and 6 months' follow-up for 19 women in Hyperbaric Oxygen Treatment initiated 1 year after breast cancer surgery with axillary lymph node dissection followed by radiotherapy. The LYCA-HBOT study, Copenhagen, 2018–2020

	Time	Mean	SD	β	95% C I	*p*-value
Total Lymph-ICF score	1 (pre HBO)	21.8	15.4			
	2 (mid HBO)	25.0	16.2	1.4	−4.7; 7.6	0.63
	3 (end HBO)	21.8	13.5	−1.8	−13.1; 9.6	0.74
	4 (3 m FU)	20.1	15.7	−3.5		
	5 (6 m FU)	15.7	14.1	−7.9	−14.8; −0.9	**0.03**
	Overall					**0.000**
Physical score subscale	1 (pre HBO)	25.3	16.0			
	2 (mid HBO)	30.6	17.8	3.1	−4.9; 11.1	0.42
	3 (end HBO)	26.1	17.6	−4.6	−12.2; 9.4	0.79
	4 (3 m FU)	22.9	16.3	−4.6	−13.9; 4.7	0.31
	5 (6 m FU)	15.1	12.6	−12.4	−19.4; −5.4	**0.00**
	Overall					**0.000**
Mobility & Movement core subscale	1 (pre HBO)	21.1	18.7			
	2 (mid HBO)	23.7	23.7	1.0	−6.4; 8.5	0.77
	3 (end HBO)	22.7	16.3	−0.0	−9.6; 9.6	0.99
	4 (3 m FU)	20.2	20.1	−2.5		
	5 (6 m FU)	15.5	14.0	−7.2	−14.7; 0.3	0.06
	Overall					**0.003**

SD, standard deviation; *B*, estimate for change in score; *CI*, confidence interval; *P*, *p*-value. Higher score is better for each domain. Scores represent a percentage of maximum score. Total = all subscales added. Time-points: 1 (pre HBO): 1 year after diagnosis- 4–8 weeks before HBOT start. 2 (mid HBO) 4 weeks into HBOT. 3 (end HBO): 8 weeks HBOT end. 4 (3 m FU) 3 months after end HBOT. 5 (6 m FU) 6 months after end HBOT. Overall: effect of time in study. Empty cells (.): statistical software unable to perform estimation

change was seen in physical measurements of LE [46]. In an RCT by Gothard et al. [18], no improvements in patient-reported QOL were found, bearing in mind that participants had long-standing chronic manifestations of LE.

There may be several reasons why we, despite patient-reported benefits, failed to see an improvement in physical measures of LE during or after the HBOT intervention. One feasible explanation is that we may not have captured the changes that were responsible for the patient-reported benefits. We measured factors related to lymphatic drainage, although the benefits may well be more strongly related to benefits from alleviating radiation-induced tissue injury. In our study, all women had undergone ALND, one of the strongest risk factors for LE [47] responsible for structural changes to the lymphatic pathways. Although it has been demonstrated that HBOT may cause neovascularization, re-organization and reduction of fibrous tissue and an increase in the number of lymphatic vessels in the sub-epithelial irradiated area [22, 23], this may not have had sufficient impact for benefits to be detected by lymphoscintigraphy, DXA and perometry, but it may be responsible for the conflicting pattern of increase in mass concurrent with improvement in symptoms and a tendency towards reduced volume and improved lymphatic drainage. Any tendency towards effect in our results may, however, be the consequence of type II error as we did not attempt a power calculation on expected effect in this explorative study.

LE has consistently been reported to negatively impact QOL [48, 49]. In breast cancer survivors in general, QOL seems to improve with time since diagnosis as a result of the natural course. However, in women with LE, the impact is more persistent, most likely because LE is a chronic and progressive condition in contrast to other sequelae after breast cancer treatments which tend to improve with time. LE severity together with younger age and anxiety has been found to be strongly associated with reduced QOL in the long term [50]. The development of treatment options that reduce the impact on QOL is therefore paramount for the growing population of breast cancer survivors at risk for LE. Due to the lack of a control group in the current explorative trial, we cannot conclude a causal HBOT effect relationship, nor can we exclude that the improvements seen might stem from the natural course of symptoms with time. However, since other studies have found that HBOT is associated to a QOL improvement for women with reduced QOL due to LE in addition to radiation-induced late toxicity, HBOT may be a relevant treatment option [17, 21, 22, 51, 52].

Table 5 Change in patient's self-reported quality of life as captured by selected subscales of the EORTC QLQ C30 and BR23 through the intervention period and 6 months' follow-up for 19 women in Hyperbaric Oxygen Treatment initiated 1 year after breast cancer surgery with axillary lymph node dissection followed by radiotherapy. The LYCA-HBOT study, Copenhagen, 2018–2020

	Time	Mean	SD	*β*	95% CI	*p*
Fatigue	1 (pre HBOT)	46.3	(31.5)			
	2 (mid HBOT)	53.8	(29.7)	7.8	−7.6; 23.4	0.29
	3 (end HBOT)	46.8	(25.9)	0.9	−3.0; 4.7	0.64
	4 (3 m FU)	42.6	(26.0)	−3.0	−40.8; 34.8	0.87
	5 (6 m FU)	29.8	(24.0)	−16.1	−33.2; 1.0	0.06
	Overall					**0.000**
Insomnia	1 (pre HBOT)	48.2	(38.3)			
	2 (mid HBOT)	38.6	(33.8)	−7.0	−23.0; 2.0	0.09
	3 (end HBOT)	31.6	(32.3)	−14.0	−30.6; −4.5	**0.01**
	4 (3 m FU)	37.0	(30.0)	−7.3	−26.8; 5.1	0.17
	5 (6 m FU)	33.3	(29.4)	−12.9	−29.2; −2.3	**0.02**
	Overall					**0.018**
Breast symptoms	1 (pre HBOT)	24.1	(17.1)			
	2 (mid HBOT)	15.0	(15.0)	−0.7	−7.0; 8.4	0.85
	3 (end HBOT)	18.0	(14.8)	−6.3	−14.9; 2.3	0.14
	4 (3 m FU)	20.2	(14.5)	−4.1	−11.3; 3.1	0.24
	5 (6 m FU)	14.9	(13.5)	−9.4	−17.1; −1.6	**0.02**
	Overall					**0.001**
Arm symptoms	1 (pre HBOT)	38.9	(25.4)			
	2 (mid HBOT)	45.6	(25.4)	5.9	−3.9; 15.6	0.22
	3 (end HBOT)	40.9	(22.2)	1.2	−12.3; 14.7	0.85
	4 (3 m FU)	37.4	(24.1)	−2.3	−14.4; 9.8	0.69
	5 (6 m FU)	28.7	(23.5)	−11.1	−25.3; 3.2	0.12
	Overall					0.063

SD, standard deviation; *B*, estimate for change in score; *CI*, confidence interval; *P*, *p*-value

For symptoms scales: higher score is worse. Scores represents a percentage of maximum score

Time-points: 1 (pre HBOT): 1 year after diagnosis- 4–8 weeks before HBOT start. 2 (mid HBOT) 4 weeks into HBOT. 3 (end HBOT): 8 weeks HBOT end. 4 (3 m FU) 3 months after end HBOT. 5 (6 m FU) 6 months after end HBOT. Overall: effect of time in study. 1st time-point has $n=18$, all others $n=19$. *EORTC QLQ C30*, European Organization of Research and Treatment in Cancer, Core module; *BR23*, breast cancer-specific module

Limitations and strengths

The small sample in the study means that only the very strong signals of change become statistically significant, and with the measurement of a large number of outcomes, the risk of changes being found by chance is high.

LE is a rather unstable condition, potentially under influence from daily variations in several external and internal factors, such as physical activity, temperature, hormonal cycle, diet and use of compression garments. We instructed participants not to wear compression garments on the day of measurements prior to the HBOT session, but we did not implement strict control during or after HBOT sessions, which may have caused an undisclosed impact on our results. Further, the participants' weight changed somewhat during the study period, which may have influenced our measurements and caused a discrepancy between single arm volume measurements (perometry) and interlimb volume difference measurements (DXA).

Although the group of patients are relatively homogenous in terms of treatment received and time since diagnosis, we were restricted by the RCT follow-up before we could invite participants into the HBOT trial. Thereby, the duration of symptoms before enrolment varied with up to 1 year. However, to the best of our knowledge, this is the most homogenous population studied in HBOT trials so far.

We had a recruitment rate of 19/50 which may be considered low. A barrier to recruitment was that only one treatment centre was available, and many patients had to travel far to participate in the extensive 8-week treatment programme. Further, many patients were reluctant to commit to an extensive treatment regime with unknown benefit, as it would interfere with getting back to normal life and picking up full-time work. Nevertheless, once enrolled, participants experienced few side effects of HBOT, and we were able to carry out a complete 6-month follow-up for all participants. Lastly, a study strength is that we used

Table 6 Change in patients' self-reported pain and lymphedema scores through the intervention period and 6 months' follow-up for 19 women in Hyperbaric Oxygen Treatment initiated 1 year after breast cancer surgery with axillary lymph node dissection followed by radiotherapy. The LYCA-HBOT study, Copenhagen, 2018–2020

	Time	Mean	(SD)	β	95% CI	*p*-value
Pain intensity in previous 24 h	1 (pre HBOT)	2.9	2.0			
	2 (mid HBOT)	3.2	2.8	0.4	−0.; 1.5	0.59
	3 (end HBOT)	2.6	2.3	−0.3	−1.6; 1.0	0.61
	4 (3 m FU)	2.5	2.8	−0.4	−1.7; 0.9	0.50
	5 (6 m FU)	1.6	2.0	−1.3	−2.4; −0.2	**0.02**
	Overall					0.065
Pain intensity in previous week	1 (pre HBOT)	1.8	2.3			
	2 (mid HBOT)	2.0	2.0	0.1	−1.4; 1.5	0.88
	3 (end HBOT)	2.1	1.7	0.2	−0.9; 1.4	0.70
	4 (3 m FU)	2.0	2.0	0.1	−0.9; 1.1	0.82
	5 (6 m FU)	1.1	1.3	−0.8	−2.0; 0.4	0.18
	Overall					0.124
Lymphedema severity previous week	1 (pre HBOT)	3.8	1.8			
	2 (mid HBOT)	3.6	2.2	−0.4	−1.3; 0.4	0.28
	3 (end HBOT)	3.3	2.5	−0.8	−1.9; 0.4	0.18
	4 (3 m FU)	2.4	1.9	−1.7	−3.0; −0.4	**0.01**
	5 (6 m FU)	2.3	1.7	−1.8	−2.7; −0.9	**0.00**
	Overall					**0.000**
Neuropathic pain score previous week (NeuPPS scale)	1 (pre HBOT)	2.1	1.5			
	2 (mid HBOT)	2.2	1.3	−0.1	−0.9; 0.8	0.91
	3 (end HBOT)	1.8	1.7	−0.4	−2.4; 1.7	0.67
	4 (3 m FU)	1.3	1.2	−0.9	−2.5; 0.6	0.20
	5 (6 m FU)	1.2	1.2	−1.0	−2.6; 0.6	0.16
	Overall					**0.000**
Fatigue previous week (FACIT-f scale)	1 (pre HBOT)*	37	2.6			
	2 (mid HBOT)	17.8	1.9	−19.7	−29.6; −9.8	**0.00**
	3 (end HBOT)	16	1.6	−21.0	−27.4; −14.6	**0.00**
	4 (3 m FU)	16.1	1.9	−20.9		**0.00**
	5 (6 m FU)	13	1.8	−24.0	−32.8; −15.3	**0.00**
	Overall					**0.000**

*Measurement was taken up to 4 months prior to HBOT start. Ranges for all scores are from 0 (no symptoms) to 10 (worst imaginable symptoms). Neuropathic pain score ranges from 0 to 5. Timepoints: 1 (pre HBOT): 1 year after diagnosis- 4–8 weeks before HBOT start. 2 (mid HBOT): 4 weeks into HBOT. 3 (end HBOT): after 8 weeks of HBOT. 4 (3 m FU): 3 months after end HBOT. 5 (6 m FU): 6 months after end HBOT. Overall: effect of time in study. 1st measurement timepoint has $n=18$, all others $n=19$. Values in bold: statistically significant *p*-values ($p<0.05$). *Time*, measurement timepoints; *Mean*, mean scores for symptoms at each measurement timepoint; *SD*, standard deviation; β, units change from baseline; *95% CI*, 95% confidence interval. Lymphedema score refers to the sensation of swelling, heaviness or tension in the breast, chest, armpit, arm, lower arm or hand on the affected side of the body. *Facit-f*, FACIT-fatigue scale. Figures in bold: statistically significant *p*-values ($p<0.05$). Empty cells (.): statistical software unable to perform estimation

only validated scales for assessing the impact of HBOT on QOL.

Conclusion

In this explorative clinical trial of HBOT in patients with LE, we demonstrate improvements in self-reported QOL in several LE-related domains, which peaked at 6 months' follow-up. The improvements could not, however, be detected in physically measured arm volume or lymphatic drainage. In women with severe symptoms of LE in addition to radiation- and chemotherapy-induced late treatment toxicity, HBOT may be a valuable treatment option. However, further research uncovering the underlying mechanisms and discriminating if certain subgroups may benefit is called upon. A large-scale, preferably blinded, multi-centre randomized controlled trial measuring overall HBOT impact on QOL in patients with severe symptoms present 12–24 months after primary breast cancer treatment seems justified.

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Data availability Data may be available by contacting the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. All participants gave written informed consent before any initiation of study activities. The trial was approved by the Danish Health and Medicines Authority as a trial including medicinal gas (EUDRACT no. 2015–000604-25), and the Ethical committee of the Capitol Region (No. R96-A6604-14-S22).

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