Short communication

Effect of hyperbaric oxygen treatment on skin elasticity in irradiated patients

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Keywords
Breast cancer; Fibrosis; Late radiation tissue injuries; Radiotherapy; Radionecrosis

Abstract
(Pandey K, Teguh DN, van Hulst RA. Effect of hyperbaric oxygen treatment on skin elasticity in irradiated patients. Diving and Hyperbaric Medicine. 2022 30 September;52(3):208–212. doi: 10.28920/dhm52.3.208-212. PMID: 36100932.)
Background: Hyperbaric oxygen treatment (HBOT) is often used in an attempt to reverse/treat late radiation-induced tissue fibrosis (LRITF). This study aimed to quantify the effects on skin elasticity.
Methods: Skin retraction time was used as a marker of skin elasticity in 13 irradiated breast cancer patients. The measurements were carried out on the affected side as well as the unaffected/healthy side at a mirrored location. Readings were taken at the start and end of HBOT (mean 43 sessions, 80 min at 243 kPa).
Results: Patient age ranged from 39–70 years. All patients underwent surgical lumpectomy and radiotherapy prior to undergoing HBOT. The mean time between radiotherapy and HBOT was 70 months. Seven of the 13 patients underwent chemotherapy. Mean irradiated skin retraction time improved from 417 (SD 158) pre-HBOT to 171 (24) msec post-HBOT ($P < 0.001$). Mean pre-HBOT retraction time in the non-irradiated skin was 143 (20) msec and did not change.
Conclusions: This promising pilot study that suggests that HBOT may improve skin elasticity in patients with LRITF.

Introduction

Breast cancer is the most common cancer in women in Europe. It represents around 25% of all types of cancers worldwide.[1] A woman with no current risk factors has a cumulative risk of 9% of getting breast cancer over a lifetime of 74 years.[1] Female breast cancer had a 5-year survival rate of 84% in 2020.[1]

Prognosis strongly depends on the stage of the cancer at the time of diagnosis. Currently, there are five known treatment options for breast cancer: surgery, radiotherapy, chemotherapy, hormone therapy and targeted therapy.[2]

Most breast cancer patients undergo multi modal therapy including radiation.[3] Repeated radiation triggers a chronic inflammatory response causing pain and discomfort. It adversely affects normal surrounding tissues, which can become hypoxic, hypocellular and hypovascular, often described as '3 H tissue'.[4] This radiation injury results in delayed and inadequate surgical wound healing.[4] In many patients, radiation and surgery is accompanied by chemotherapy. This combination though, increases the severity of late radiation induced tissue fibrosis (LRITF).[5]

Current therapies for LRITF include hyperbaric oxygen treatment (HBOT), anti-inflammatory treatment with corticosteroids or interferon gamma, vascular therapy with pentoxifylline and antioxidant treatment with dismutase, pain management with medication, physiotherapy and oedema therapy.[6]

Late radiation-induced effects, as discussed in this study, are defined as occurring at least three months after the use of radiation.[7] HBOT has long and short term effects on LRITF.[8] Short-term effects include oedema reduction, phagocytosis activation, and anti-inflammatory effects.[8] Long-term effects include neovascularization, osteoneogenesis, and stimulation of collagen formation by fibroblasts.[9] HBOT induces significant angiogenesis and mobilisation of stem cells from the bone marrow, leading to wound healing and recovery of radiation injury.[2] HBOT creates a steep oxygen gradient from the atmosphere to the patient's body making large amounts of dissolved oxygen available in tissues fueling angiogenesis and improving white cell and fibroblast function.[10,11]

Breast cancer patients receiving HBOT for LRITF have reported improvements in quality of life, functionality

and lower pain scores.[10] These outcomes are based on patient-reported outcome measures (PROMS), without any objective assessment. In the absence of objective outcome quantification, it is difficult to include HBOT as a standard form of treatment for LRITF management.

In this pilot study we aimed to objectively measure the effect of HBOT on LRITF by quantifying skin-elasticity using the DermaLab® suction cup (Cortex Technology, Hadsund, Denmark) which has been used for measuring skin-elasticity as well as radiation fibrosis in the past.[12,13]

Methods

The Medical Ethics Committee affiliated with the Amsterdam University Medical Center approved our methods of handling personal details and privacy and concluded that they were concordant with the guidelines of the Association of the Universities in the NL and declaration of Helsinki.

This was a prospective pilot study quantifying the effects of HBOT on LRITF. Breast cancer patients, from a variety of racial/ethnic groups, treated with surgery followed by radiation, and with complaints of LRITF were included. The study was conducted from May to December 2020. Informed consent was obtained before commencement of HBOT. Patients were chosen on a voluntary basis and were free to opt out at any point during the study.

HBOT consisted of 43 sessions on average: one session a day, five days a week for eight weeks. Each session lasted 115 minutes. The subjects breathed 100% oxygen at 243 kPa (2.4 atmospheres absolute [atm abs]) for a total of 80 minutes (four 20-minute periods with intervening five-minute breaks during which they breathed air).

The skin-elasticity of the area affected with LRITF was measured using the commercially available skin testing device DermaLab Suction Cup® (Cortex Technologies, Denmark) through skin retraction time, an inverse measure of skin-elasticity: the higher the skin retraction time, the lower the elasticity. A vacuum probe on the skin measured the stress necessary to achieve a given transformation.[12] Although the device provided multiple derived variables, this study considered the directly measured variable of skin retraction time.[14] The location with the most pain, discomfort and the subsequent highest retraction time was chosen as the measurement site.

The measurements were carried out at the start and end of HBOT on the irradiated breast (test) as well as a mirror location on the non-irradiated breast (control). Each measurement was carried out thrice and the mean was used for data tabulation.[15] The test and control locations were marked with a permanent marker.

A paired Student's *t*-test was carried out using Microsoft Excel (Version 14.4.1) to test the difference between pre- and post-HBO_2 skin retraction time. Data were reported as mean (standard deviation [SD]), and a *P*-value of < 0.05 was considered to be significant.

Results

The study group consisted of 13 women ranging from 39 to 70 years of age, with a mean age of 56 years (Table 1). Four underwent 40 HBOT sessions, five underwent more than 40 sessions, and four less than 40 sessions. The lowest number of sessions completed was 35. One patient was retreated (after earlier HBOT in 2019) due to a recurrence of LRITF-associated problems. The average number of sessions was 43.

At the start of treatment, the skin retraction time at the irradiated site was significantly higher than the control site. There was a significant reduction in skin retraction time for the irradiated site at the end of HBOT compared to that at the start. Skin retraction time for the control area did not change significantly over the course of HBOT. The results showed a significant improvement in radiation-site

Table 1
Demographic and clinical characteristics of the study population

Characteristics of Study population (*n* = 13)	
Age (years)	
Mean	56
Median (range)	54 (39–70)
Radiotherapy	
Yes	13
No	0
Time since radiotherapy (months)	
Mean	70
Median (range)	54 (8–247)
Maximum radiotherapy dose (Gy)	
Mean	55.2
Median (range)	55.9 (50–55.9)
Chemotherapy	
Yes	11
No	0
Unknown	2
Surgery (Lumpectomy)	
Yes	13
No	0
Unknown	0

Table 2
Pre- and post-HBOT skin retraction times (in milliseconds)

Patient	Radiated breast		Non-radiated breast		HBOT sessions (*n*)
	Pre-HBOT	Post-HBOT	Pre-HBOT	Post-HBOT	
1	481	161	121	114	36
2	326	149	120	121	50
3	514	201	180	180	49
4	346	167	146	148	36
5	314	151	144	144	38
6	762	176	123	124	40
7	386	146	145	146	47
8	263	158	147	145	40
9	222	174	161	167	40
10	262	162	143	143	60
11	292	147	174	173	40
12	687	226	122	115	35
13	446	199	131	135	50
Mean (SD)	417 (158)	171 (24)	143 (20)	143 (21)	43 (7)
Δ Retraction time	246.00		0.15		
***P*-value**	$P < 0.001$		$P = 0.8824$		

skin-elasticity (reduction in skin retraction time) of all post-radiation therapy breast cancer patients included in this pilot. The improvement in skin-elasticity was statistically significant ($P < 0.001$) (Table 2). There were no HBOT related complications in this study.

Discussion

This pilot study shows that HBOT may significantly improve skin-elasticity in breast-cancer patients with LRITF. All 13 patients in this study showed an increase in skin-elasticity. Radiation induces fibrosis of the skin and underlying tissue, causing loss of local function, pain and discomfort. The objective measurements suggesting improvement in skin-elasticity following HBOT reported here indicate its effectiveness in the management of LRITF.

Worldwide, radiation therapy is a part of the multimodal breast cancer treatment, reducing local recurrence and increasing disease-free survival.[16,17] It frequently results in thickening, fibrosis, and inflammation of the irradiated skin as a consequence of radiation-induced tissue toxicity.[18] This often results in severe fibrosis and pain. Fibrosis may also lead to altered breast appearance causing severe psycho-sexual consequences.

Irradiation as described above can result in substantial thickening of the skin and damage of deeper structures (such as muscle) as a result of fibrosis.[19] This widespread fibrosis can lead to pain, discomfort and a reduced quality of life.[20] Chronic effects of LRITF include fibrosis, skin atrophy and ulceration with impaired healing. HBOT in this group of patients can not only help with improvement in pain, fibrosis, and oedema, but also be used pre- and post-procedure for future breast related cosmetic surgery.[3,21]

There have been a multitude of therapeutic options described for the management of post-radiation fibrosis including physical massage, use of antioxidants, use of superficial lotions and gels, and fat grafting of the affected area. HBOT is an approved option for radiation-induced fibrosis and is widely used to aid wound healing, reduce fibrosis, reduce pain and discomfort related to LRITF.[3] HBOT promotes tissue regeneration and wound healing with the help of local and systemic effects.[18] It seems to do this through a series of changes in tissues such as hypoxia reversal, radical stress and lactate concentration.[22] These stimuli result in release of vascular endothelial growth factors, promoting new blood vessel formation. Additionally, oxygen delivery also aids in white cell and fibroblast recruitment, further aiding wound healing. As with many therapies, HBOT is not free of risks, but it is relatively safe with a very low complication rate.[23] Occasionally it can cause side effects such as barotrauma, central nervous system and pulmonary oxygen toxicity and hyperoxic myopia.[8,23] Middle ear barotrauma is one of the most common issues.[23]

LRITF is strongly related to the cumulative radiation dose.[18] The average radiation given to the patients in this study is consistent with the doses required to cause LRITF.[13] Previous studies have shown that LRITF of swallowing muscles was observed when a radiation dose of 46–70 Gy was given.[24] In this study however, there appeared to be no correlation between the amount of radiation received and baseline skin elasticity in the damaged breast. This could partly be due to the small variance in the radiation dosage used.

Quantification of retraction times could play an important role in assessing superficial-induced fibrosis. Few relevant data are available. One study showed the mean healthy skin retraction times in the upper arm to be 392 ms.[25] While this value is higher than the values we observed for healthy skin retraction times, it is important to note that this study only measured retraction times for the arm. Furthermore, previous studies also show that with an increase in age, a decrease in skin elasticity is observed.[26]

Being a pilot study, it had its own limitations in the form of a small population, a lack of controls and variable time between the end of radiotherapy and the start of HBOT. A key limitation related to the DermaLab method was the fact that it did not measure deep-situated tissues.[27] As the maximum suction that the DermaLab could apply was only 15.625 millipascal, retraction times for deeper situated tissues could not be measured.[27]

The small study population is a limitation. A larger definitive study could be designed using a power calculation based on the present data to ensure that the appropriate number of participants have been chosen. A control group consisting of similar patients who did not undergo HBOT would be added. Future projects investigating the quantitative as well as qualitative effects of HBOT would be optimal in order to shed more light on the efficacy of HBOT in this group of patients.

Conclusion

In conclusion, this promising pilot study has shown that HBOT may provide benefit in patients suffering from LRITF. Despite numerous medical advances in the past decade, measuring fibrosis and the rate of fibrosis remains a challenge. The DermaLab device has proven to be a reliable apparatus in terms of measuring LRITF. A prospective controlled trial using PROMS along with quantitative measurements through the use of DermaLab Suction Cup is currently in preparation at our center.

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Conflicts of interest and funding: nil

Submitted: 7 January 2022
Accepted after revision: 6 May 2022