

Quality of life – The effect of hyperbaric oxygen treatment on radiation injury

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ABSTRACT

The purpose of the present study was to assess changes in health-related quality of life (HRQL) among patients with radiation injury one year after hyperbaric oxygen (HBO₂ therapy). HBO₂ therapy was given once daily, five times a week in monoplace hyperbaric chambers for at least 19 days. HRQL was measured by SF-36 (Short Form with 36 questions). The study population was 101 patients, and among these 53.5% had radiation injury to the head and neck region, 35.6% to the intestine and 10.9% to the bladder. Testing for differences before and one year after HBO₂ therapy showed significant improvement for the following SF-36 scales:

- *Physical Function* an increase of 4.54 ($p = 0.01$)
- *Role Performance* an increase of 8.79 ($p = 0.04$)
- *Vitality* an increase of 6.88 ($p = 0.001$)
- *Social Function* an increase of 8.04 ($p = 0.002$)

Time since radiation at HBO₂ therapy was 1-39 years. A total of 82% received radiation more than one year ago, and 33 % more than seven years ago. Changes in physical and mental sum scores were not associated with time since radiation. Patients below the age of 70 seemed to have the best effect of HBO₂ therapy measured by HRQL.

INTRODUCTION

Radiotherapy, used in the treatment of certain malignant tumors, causes a hypoxic, hypocellular and hypovascular environment that might injure surrounding normal tissue. Acute radiation reactions are common. Some patients suffer, however, from late radiation injury.

Reuter *et al.* [1] reported osteoradionecrosis in 8.2% of all head and neck tumor patients who received radiotherapy. Xerostomia is a common problem among head and neck patients [2]. Harris *et al.* [3] showed an increase during the last years. Among gynecological cancer patients, radiation-related complications of 5%-15% have been reported [4], while late side effects of proctitis between 2.5% and 25% have been reported by some authors [5-6]. Patients with radiation injury often show substantial reductions in health-related quality of life (HRQL) [7-13].

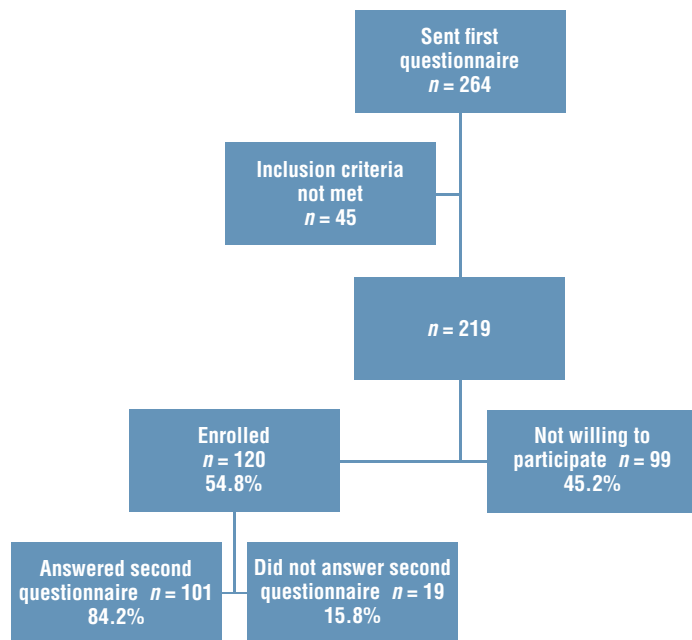
Hyperbaric oxygen (HBO₂) therapy is used to treat these side effects by increasing the tissue oxygen pressure repetitively and thereby stimulating neoangio-

genesis [14], the purpose of which is to enable the hypoxic tissue to re-establish some of its former functions. Although this therapy is widely applied, its mechanism of action is still poorly understood, and controversy exists in the literature about its clinical use [8,9,15]. To what degree HBO₂ therapy has an effect on HRQL is sparsely documented [10,11,16]. However, a small recently published study showed an effect of HBO₂ therapy on HRQL in maxillofacial patients [17].

The purpose of the present study was to assess possible effects on HRQL in patients with radiation injury one year after HBO₂ therapy.

PATIENTS AND METHODS

This observational study included radiation-injured patients treated at The Hyperbaric Medical Unit (HMU) at the Department of Occupational Medicine, Haukeland University Hospital in Bergen, Norway. HMU performs all planned HBO₂ therapy in the country. Eligibility criteria for this study were patients given HBO₂ therapy at HMU during the period from October

FIGURE 1. Flow chart of potential study participants

2007 to November 2010 due to radiation injury to the head and neck region, bladder or intestine. Patients were enrolled in the study if they fulfilled the inclusion criteria:

- age 18-80 years
- spoke Norwegian fluently
- gave their written consent to participate in the study

Patients who had completed fewer than 19 HBO₂ therapy sessions and patients who, during the year after inclusion, had received additional HBO₂ therapy or surgical intervention were excluded.

Altogether 264 patients were invited, although some of these had to be excluded since they did not fulfill the inclusion criteria, and some refused to participate (Figure 1). A total of 101 of the enrolled patients (84.2%) returned a second SF-36 questionnaire one year after HBO₂ therapy. Among these, 53.5% had radiation injury to the head and neck region, 35.6% to the intestine and 10.9% to the bladder. None had to be excluded due to surgery or additional HBO₂ therapy.

All patients received outpatient treatment in mono-place hyperbaric chambers (ETC, Baramed), where they breathed 100% oxygen at a pressure of 2.4 atmospheres absolute (atm abs) for 90 minutes. This was administered in three oxygen breathing periods of 30 minutes each, separated with a five-minute air break. The treatment

was given once daily, five times a week, and all patients received between 19 and 60 treatments. A total of 52% of the patients had received 19 to 29 treatments, 30% 30 to 39, and 18% 40 to 60 treatments.

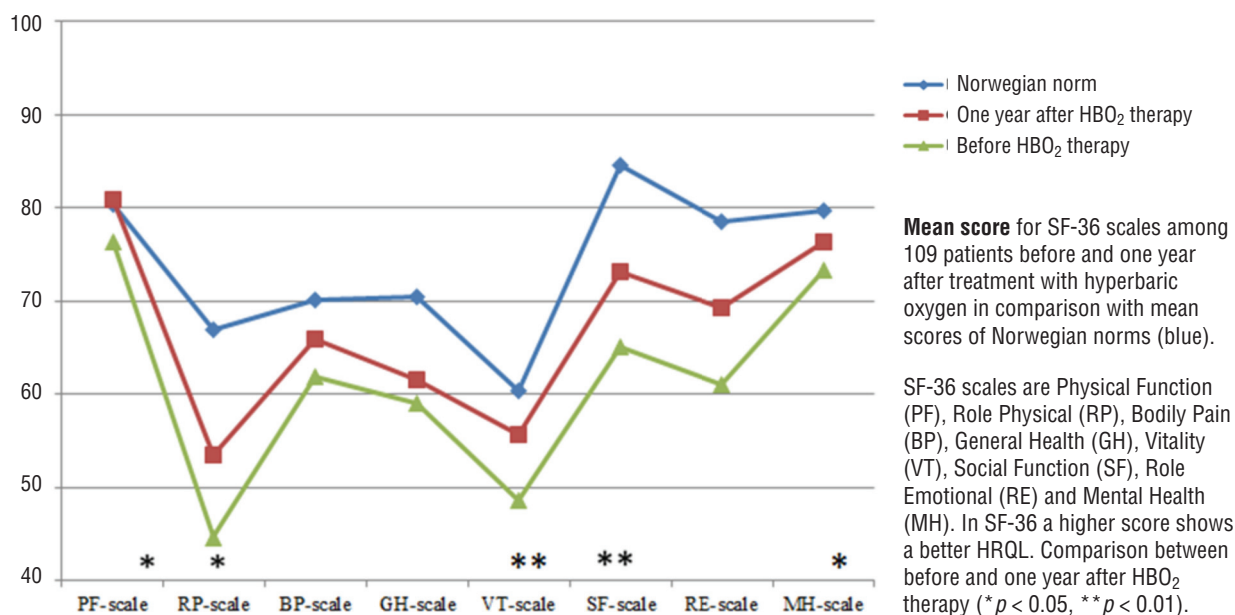
The participants were asked to complete the SF-36 questionnaire shortly before the first HBO₂ therapy began. The first 80 patients received the questionnaire and a stamped return envelope by mail. One reminder was given. The remaining 184 patients received the questionnaire at the HMU information meeting before the first treatment, and were asked to return the questionnaire at HMU the next day. No reminder was given. One year after the last HBO₂ therapy session, all enrolled patients were asked to fill out SF-36 once more, and to provide information about the time since radiation and surgeries during the last 12 months. The questionnaire was sent by mail, together with a stamped return envelope. One reminder was given.

The SF-36 is a well-documented, self-administered HRQL scoring system. Based on 36 questions, eight independent scales and two main dimensions are created for each person. All scales are further standardized (0-100). SF-36 has been widely used, validated and translated into several languages, including Norwegian [18]. The scales Physical Function (PF), Role Physical (RP) and Bodily Pain (BP) are measurements of functional health and well-being scores. Psychometrically based physical and mental health summary measures are General Health (GH), Vitality (VT), Social Function (SF), Role Emotional (RE) and Mental Health (MH). In SF-36 a higher score shows a better HRQL. Summary measures of Physical Health and Mental Health based on SF-36 were calculated as well. No reference group was included in this study. However, comparison with the Norwegian reference for SF-36 is made.

Statistical methods

Potential changes in HRQL one year after HBO₂ therapy were tested by a mixed effects model for each of the eight SF-36 scores adjusted for gender and age. Effects of the time span between radiation and HBO₂ were tested similarly. Differences in HRQL among the patients enrolled (filled in questionnaires once or twice) were tested by one-way univariate ANOVA for

FIGURE 2. Mean scores of patients vs. norms



physical and mental health (summary measures). For all analyses, PASW Statistics 18.0. (SPSS) was used.

The study was approved by the Research Ethics Committee (registration number 17276). All patients included in this study gave their written consent to participate.

RESULTS

Fifty-six (55.4%) men (mean age 62.8, SD 8.5) and 45 (44.6%) women (mean age 59.3, SD 12.1) were enrolled. Years since radiation were one to three for 28.7% of the enrolled patients, four to 10 for 55.5% and more than 10 for 15.8%.

The data show (Figure 2) a tendency for improved HRQL for all SF-36 scales one year after HBO₂ therapy.

The following SF-36 scales showed significant score improvement one year after HBO₂ therapy:

- Physical Function (PF) an increase of 4.54 (95% CI 1.1-8.0; $p=0.01$)
- Role Performance (RP) an increase of 8.79 (CI 0.2-17.4; $p=0.04$)
- Vitality (VT) an increase of 6.88 (CI 2.8-11.0; $p=0.001$)
- Social Function (SF) an increase of 8.04 (CI 3.1-12.9; $p=0.002$)
- Mental Health (MH) an increase of 3.09 (CI 0.2-6.2; $p=0.048$)

Except for MH, adjustment for gender and age did not alter significant findings.

Since quality of life may vary among the groups of patients, we separately studied the patients with radiation injuries to the head and neck region, bladder and intestine. Scores before HBO₂ therapy and changes in all SF-36 scales are shown in Table 1.

Changes in physical and mental scores (summary measures), adjusted for gender and age, were not associated with time since radiation. The effect of HBO₂ therapy on HRQL among age groups based on first, second, and third quartile varied (Figure 3); however, for most groups there was a tendency for improvement.

The youngest age group (18-54 years) had a significant improvement in Physical Function (PF) ($p = 0.007$) and in Bodily Pain (BP) ($p = 0.03$). In the age group 55-63, significant improvement was seen for the scales Social Functioning (SF) ($p = 0.002$) and Mental Health (MH) ($p = 0.046$). Ages 64-69 showed improvement in Role Performance (RP) ($p = 0.02$), General Health (GH) ($p = 0.046$) and Vitality (VT) ($p = 0.02$). For the group above the age of 69 years, no improvements were seen for any HRQL scales. Figure 3 shows variation among age groups with no improvement in the oldest age quartile. However, both Norwegian norms, pre- and post-HBO₂ therapy are close, which indicates that the older age group is quite stable regarding SF-36, and changes within a year are difficult to detect.

TABLE 1. SF-36 scales before hyperbaric oxygen treatment and change one year after treatment according to type of radiation injury

Type of radiation injury	SF-36 scale	Score before HBO ₂ therapy	Change in score after one year	Crude <i>p</i>	Adjusted <i>p</i> *
Bladder	Physical Function (PF)	68.2	+8.6	ns	ns
	Role Physical (RP)	29.7	+4.3	ns	ns
	Bodily Pain (BP)	59.8	+12.5	ns	ns
	General Health (GH)	54.7	+5.7	ns	ns
	Vitality (VT)	46.3	+5.9	ns	ns
	Social Function (SF)	55.7	+20.5	0.07	0.053
	Role Emotional (RE)	33.3	+48.5	0.007	0.01
	Mental Health (MH)	71.2	+6.9	ns	ns
Head and neck	Physical Function (PF)	80.3	+2.3	ns	ns
	Role Physical (RP)	57.2	+4.9	ns	ns
	Bodily Pain (BP)	66.3	+4.8	ns	ns
	General Health (GH)	64.3	+0.08	ns	ns
	Vitality (VT)	53.0	+2.5	ns	ns
	Social Function (SF)	69.0	+7.9	0.02	0.02
	Role Emotional (RE)	64.9	+2.6	ns	ns
	Mental Health (MH)	74.0	+2.1	ns	ns
Intestine	Physical Function (PF)	72.9	+6.4	0.05	0.02
	Role Physical (RP)	39.9	+16.1	0.04	0.04
	Bodily Pain (BP)	59.0	+0.1	ns	ns
	General Health (GH)	54.5	+3.7	ns	ns
	Vitality (VT)	43.2	+13.7	<0.001	0.001
	Social Function (SF)	62.1	+4.4	ns	ns
	Role Emotional (RE)	65.6	+4.3	ns	ns
	Mental Health (MH)	71.6	+3.4	ns	ns

* Adjusted for gender and age

No differences were seen in HRQL before HBO₂ therapy between 19 patients who were enrolled but lost at follow-up, and those taking part in the entire study.

Among the 99 patients who refused to join the study, 56.0% had radiation injury to the head and neck region, 24.2 % to the intestine and 19.8% to the bladder. When the data collection was finished, mortality was 8.8% among patients not included and 8.7% in the enrolled patients.

DISCUSSION

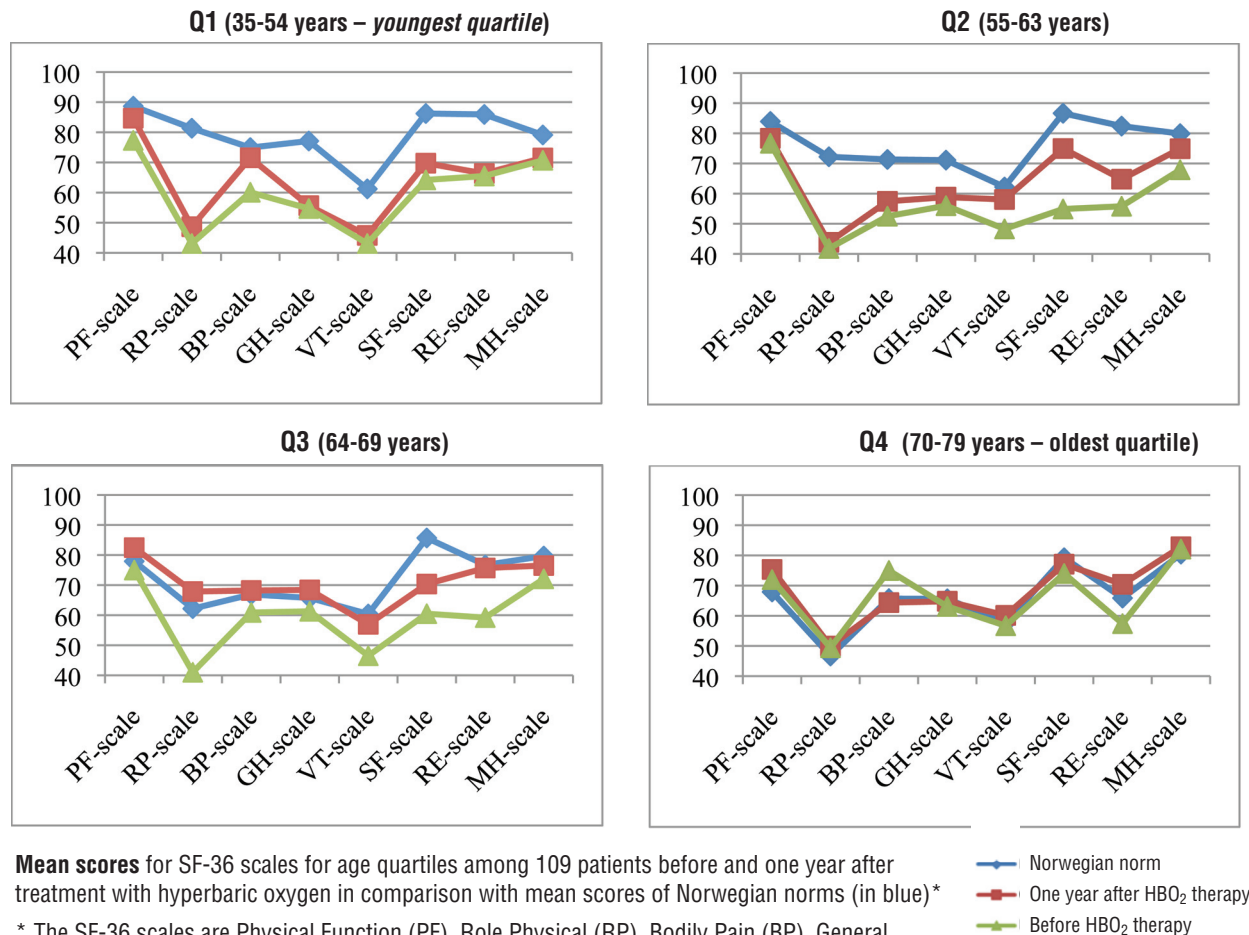
For the total group, the scales Physical Function (PF), Social Function (SF) and Vitality (VT) had improved one year after HBO₂ therapy. The youngest age group (18-69) seemed to show an effect on HRQL. In the oldest age group SF-36 was quite stable. No differences were seen between norms, and scores before and after HBO₂ therapy.

Patients with radiation-injured head and neck region had improved Social Function (SF), patients with injured intestine had improved Physical Function (PF),

Role Performance (RP) and Vitality (VT). Patients with injured bladder had improved Social Function (SF) and Role Emotional (RE). However, statistically significant findings are not always clinically relevant. Several of the changes in this study are not clinically significant based on reliable change index [19]. However, for the total population, the SF-36 profiles show consistent improvement for all scales.

This was a fairly large study of HBO₂ therapy on radiation injury in a population within a short time span. The patients had been treated at hospitals all over Norway, and had various types and degrees of radiation injury. Potential hospital differences could be adjusted for partly by the study design since patients were their own control. As opposed to multicenter studies, we could assure that all patients received the same type of HBO₂ therapy at HMU. Questionnaires were distributed to all patients with radiation injury to the head and neck region, bladder or intestine. The medical doctors at HMU were not aware if the patients were included in the study or not.

FIGURE 3. Mean scores of patients vs. norms



Several of the patients were not willing to participate. In Norway the participation rate in questionnaire studies has been decreasing since the 1980s. The Norwegian HUNT study, a three-part longitudinal population health study, showed decreasing response rates from 90% in 1984-86, to 70% in 1995-97 and slightly above 50% in 2006-08 [20].

Of the patients enrolled in the present study, 19 did not return the second SF-36 questionnaire. No significant differences in quality of life were seen before HBO₂ therapy for patients who had answered the SF-36 once or twice, and a selection bias is not likely.

We chose to invite all patients who met the inclusion criteria to participate and made no random selection. No blinding was done in this study. Blinded groups receiving either sham or HBO₂ therapy are preferable,

but difficult to accomplish. A double blinded randomized controlled multicenter trial on the effect of HBO₂ therapy on radiation cystitis (HORTIS III) [21] in Norway was terminated prematurely last year due to poor recruitment of patients. Most patients are reluctant to enter a trial where they could risk spending an extra month away from home due to received sham treatment.

Due to lack of blinding and sham treatment in this study, we cannot be sure if the changes in HRQL one year after HBO₂ therapy were caused by HBO₂ therapy or other factors as, for instance, spontaneous recovery. Patients with injured intestine had improved Physical Function (PF), Role Performance (RP) and Vitality (VT). The results fit with our clinical experience due to improved diarrhea.

Unfortunately information on background data on

radiotherapy, chemotherapy, smoking status, cancer stage and localization are not available. The authors discussed whether it was possible to get more information from the patient records at HMU, but concluded that this could not be done in a standardized way.

We chose to use the non-organ-specific instrument SF-36 since the object was to study radiation injury for several organs, as well as compare patient groups. Previous studies have used several types of HRQL instruments, including organ-specific instruments. Unfortunately additional HRQL questionnaires, *i.e.*, EORTC, were not included in our study. Harding *et al.* [16] concluded that organ-specific instruments could be used to evaluate HRQL; and they state: “The lack of significant changes in this study using the SF-36 may be due to the global nature of the questionnaire and the changes experienced by the participants are attributable to the combination of surgery and HBO₂ therapy.”

In our study none of the patients underwent surgery relevant to their illness after they had completed the HBO₂ therapy session.

Even if spontaneous recovery of salivary glands can occur in patients who received HBO₂ therapy 0-2 years after radiation therapy (RT), this might not influence the results in this study. When the second questionnaire was answered, 86% of the patients had received RT more than two years prior.

Which time interval after HBO₂ therapy is best for evaluating effect? Our experience during several years tells us that most improvement is seen during the first year after HBO₂ therapy, which is why we chose to evaluate the effect one year after HBO₂ therapy.

A review from 1999 [22] stated that HBO₂ therapy based on HRQL is not beneficial for radiation-injured bladder. Our study also saw effects of HBO₂ therapy in this group of patients. Unfortunately the study design in this and most studies regarding HBO₂ therapy and HRQL have their limitations. With exceptions [4], few randomized double-blind studies have been carried out. Various sham treatments have been used. It is important to choose a safe and undetectable sham treatment.

In this study HRQL was used as a proxy for improved functions after HBO₂ therapy. Our data show that the effect of HBO₂ therapy one year after treatment seems to have a positive impact on health-related quality of life for the total population. However, we saw no effects of HBO₂ therapy in the upper-age quartile. This fact will dilute the finding for the total group. For effects on various patients and age groups, more studies have to be done.

The authors report that no conflict of interest exists with this submission. ■

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