PATHOLOGY

Effects of Hyperbaric Oxygen Therapy on Quality of Life in Maxillofacial Patients With Type III Osteoradionecrosis

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Purpose: Over a 4-year period, 18 patients with type III osteoradionecrosis that developed an average of 55 months after radiotherapy treatment for head and neck cancers were referred for hyperbaric oxygen therapy (HBO_2).

Materials and Methods: Participants completed a questionnaire battery before and after HBO_2, including the European Organization for Research and Treatment of Cancer (EORTC) Core 30, the EORTC Head and Neck 35, and the Medical Outcomes Short Form 36.

Results: The EORTC Core 30 questionnaire indicated significant improvements in "emotional functioning" and "insomnia" ($P \leq .01$ and $P \leq .01$). An improvement also was found in the "social eating" ($P \leq .01$) and "teeth" ($P \leq .01$) domains of the EORTC Head and Neck 35 questionnaire. These beneficial outcomes might be explained in part by the social environment of being in a specific treatment group with similar patients. However, the Medical Outcomes Short Form 36 indicated a significant decrease in "social functioning" ($P \leq .01$). The patient group in this study did not undergo any surgical intervention between the 2 time points and no other interventions could be connected with the improvements, particularly in relation to "teeth." In addition, clinical follow-up confirmed the stabilization of the patients' clinical conditions.

Conclusions: The findings of this study support the hypothesis that HBO_2 has positive physiologic and psychological effects on some factors for this patient group.

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Maxillofacial carcinomas are the eighth most common form of cancer in the UK population.[1] Surgery, radiotherapy, and chemotherapy alone or in combination are the main treatment modalities. Despite the life-saving abilities of these treatments, there are some serious side effects. These include mucositis, fibrosis, xerostomia, trismus, and, in approximately 2% of cases, osteoradionecrosis (ORN) and soft tissue radionecrosis.[2] These side effects are, for the most part, deemed irreversible and have a significant demonstrable negative effect on a patient's quality of life (QoL).[3] In some cases, surgery is considered part of the long-term treatment of the patient, but surgical intervention in a heavily irradiated field may result in delayed wound healing, dehiscence, or infection.[4,5] These factors combined with a patient's other comorbidities affect consultants' decisions on ongoing treatment.

Hyperbaric oxygen therapy (HBO_2) is increasingly accepted as a treatment for radiation proctitis,[6] and it has been suggested as a medical treatment for soft tissue radionecrosis in other parts of the body.[7-9] However, HBO_2 is not generally used as a stand-alone treatment for ORN because dead bone needs to be removed surgically.

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ORN develops in 3 well-established clinical scenarios and produces 3 types: type I occurs when teeth are removed from a jaw to be radiated and fewer than 21 days are allowed for tissue recovery and healing before commencing radiotherapy; type II occurs years after radiotherapy and is a result of external or surgical trauma; and type III occurs spontaneously after radiotherapy and is not related to any trauma.[10] In maxillofacial patients with types I and II ORN, HBO_2 is used in a regime that sandwiches surgery according to the Marx protocols,[11-14] and this treatment modality has been shown to have a positive effect on QoL.[15,16] In the present research, the authors were interested in type III ORN, ie, that which occurs spontaneously. Whatever the presentation, surgeons are generally keen to avoid or minimize surgery, if possible, because of the potential to exacerbate the problem and the patients' comorbidities.

In this report, the authors describe the changes in QoL reported in a questionnaire battery by patients undergoing HBO_2 as a treatment for type III ORN.

Materials and Methods

ETHICS

Ethical approval was granted from the local research ethics committee according to British Psychological Society guidelines and the Declaration of Helsinki. The study was explained to potential recruits from an information sheet and questions were answered. Written consent was obtained.

PARTICIPANTS

Eighteen patients (13 men; mean age, 63.6 yr) referred for HBO_2 after radiotherapy for head and neck cancer (HNC) were recruited to complete a questionnaire battery before and after HBO_2. The questionnaires before HBO_2 were completed after a medical assessment for fitness to undertake HBO_2 and before a patient's first treatment on the same day. The questionnaires after HBO_2 were undertaken after the last HBO_2 before formal discharge from the hyperbaric unit. There was an average of 28 days between these 2 time points.

The average body mass index for the participants was 24.17 kg/m^2 (standard deviation, 4.01 kg/m^2), which is within the "normal" range. Demographic data were collected from the patients' hyperbaric medical notes and are presented in Table 1. Table 1 also includes the referring consultants' review of the patients' status 2 years after HBO_2 had been completed.

INCLUSION AND EXCLUSION CRITERIA

All patients were older than 18 years and had English as their first language. None of the patients had previously undergone HBO_2. Patients were referred with type III ORN that had been confirmed by orthopantomogram and clinical examination. Referral was made to minimize the need for surgical intervention.

HBO_2 REGIME

Patients received 29 to 49 therapies (mean, 34.0; standard deviation, 6.1) in a multiplace chamber at the Hyperbaric Medical Centre (Plymouth, UK). All participants underwent HBO_2 twice a day at 2.2 Atmospheres Absolute (12 m) for 45 minutes, an air break for 5 minutes, and then another 45 minutes (in total, 90 min breathing 100% oxygen) for 5 days a week (Fig 1). The daily treatments were separated by a minimum of 3.5 hours. Oxygen was delivered through an Amron Oxygen Treatment Hood (Vista, California) or a Sea-Long Series 7000 Mask (Louisville, Kentucky).

THE QUESTIONNAIRE BATTERY

Currently, there are no QoL questionnaires designed specifically for use in hyperbaric medicine. The measurements used in this research were developed and validated in settings such as outpatient clinics and in the hospital environment and therefore were deemed valid and appropriate for the assessment of change in this study. Two questionnaires were used: the Medical Outcomes Short Form 36 (SF-36)[17] and the European Organization for Research and Treatment of Cancer (EORTC)[18] Core 30 (QLQ-C30) with its subscale, the EORTC Head and Neck 35 (QLQ-HN35).[19] These questionnaires were outlined in a previous article that assessed patients with HNC undergoing HBO_2 perioperatively.[16]

The participants completed the questionnaires independently and unsupervised.

ANALYSIS METHOD

The primary statistical method used in this research was the Wilcoxon sign-rank test because of the small sample. To account for the number of subscales within the measurements used, statistical significance was set to $P \leq .01$.

Results

Participants had completed their cancer treatment on average 55 months before starting their HBO_2.

Using the SF-16, improvements (although not to a significant level) were found across all domains except for "social functioning," which showed a significant decrease (Table 2).

Significant changes were evident using the EORTC QLQ-C30 (Table 3) in "emotional functioning" and "insomnia." As with the SF-36, most subscales showed

Table 1. DEMOGRAPHIC DATA

Patient Number	Gender	T	N	M	Number of HBO_2 Treatments	Absorbed Radiation (Gy)	Time Since Radiotherapy (mo)	Smoking (Cigarettes/day)	Alcohol (U/wk)	BMI on Admission	Referring Clinicians' Outcome Reports 2 yr After HBO_2
1	Female	—	—	—	30	76	72	0	0	25	No requirement for surgical intervention
2	Male	2	0	ND	36	55	23	10	0 (reformed alcoholic, quit 5 yr previously)	24	Did very well but within 6 months needed surgery
3	Male	4	0	ND	36	60	18	>20	10-20	21	ORN stabilized, no surgery needed
4	Male	1	0	0	36	60	12	>20	20-40	27	ORN showed good response, stable
5	Male	4	1	ND	30	54	48	Quit 4-5 yr previously	1	22	ORN stable, no surgery planned
6	Female	4	2	ND	35	60	30	Quit 1-5 yr previously	—	—	ORN did very well
7	Female	—	—	—	38	—	192	20 before quitting 16 yr previously	Occasional	21	ORN stabilized, no surgery planned
8	Male	2	0	ND	38	—	120	0	14	25	ORN stable but needed minor debridement
9	Male	2	1	ND	29	—	12	15-20	—	22	ORN stable but needed surgery and HBO_2 2 yr later
10	Male	1	0	ND	40	60	56	Quit pipe smoking 4 yr previously	18	26	ORN stabilized, no surgery required
11	Male	2	0	ND	29	—	60	4	Occasional	—	ORN showed good outcome but remains with problems
12	Male	4	2	ND	30	—	49	10	3	20	ORN stabilized, no need for surgery
13	Male	1	1	ND	29	—	96	Quit 22 yr previously	0	35	Minor debridement required
14	Female	—	—	—	29	42	84	—	—	—	ORN appears to be stable
15	Male	2	0	ND	30	—	60	2	3	19	ORN did well but developed recurrent cancer 18 mo later
16	Male	1	0	0	46	90	36	Quit 20 yr previously	Occasional	29	ORN did well but required surgery some 18 mo later
17	Male	4	0	ND	29	—	18	0	1	23	ORN stabilized, no need for surgery
18	Female	4	0	ND	49	50	7	0	Very occasional	26	ORN stabilized, no need for surgery

Abbreviations: —, data not provided by referring clinician; BMI, body mass index; HBO_2, hyperbaric oxygen therapy; M, metastatic stage; N, nodal stage; ND, not determined; ORN, osteoradionecrosis; T, tumor stage.

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improvement trends but did not reach significance at $P \leq .01$.

This pattern of improvement continued in the domains of the EORTC QLQ-HN35, where significant amelioration in the domains of "social eating" and "teeth" were found (Table 4).

Discussion

QoL measurements have been used widely in the assessment of patients with HNC malignancy. They are a valuable tool because these cancers and the treatment that patients receive can have a significant impact on individuals' QoL.

Given the number of variables previously shown to have an impact on health-related QoL in this patient group and the variation between patients and missing data,[3] it is not surprising that so few factors reached significance in this study. However, the trend throughout the data of an improvement does suggest a beneficial effect of HBO_2 on QoL.

As with the patients in this study (Table 1), it is sometimes reported to Diving Diseases Research Centre (DDRC) that patients referred for HBO_2 have not undergone surgery owing to a significant improvement in their condition. This explains the spread of the number of treatments in those having 29 to 30 being referred for pre- and postoperative HBO_2 and not returning to DDRC for postoperative treatment because the referring consultants judged that surgery was unnecessary. Those participants having more than 30 therapies were those returning for what would have been postoperative treatments, but were actually therapies to consolidate healing without surgery. The "preoperative" series of HBO_2 had improved the patients' condition to the extent that the referring consultants did not want to operate but judged some further HBO was needed.

Because of the nature and workload of the hyperbaric unit where these data were collected (charity outside the National Health Service, UK), it is often difficult to obtain all the patient data that are re-

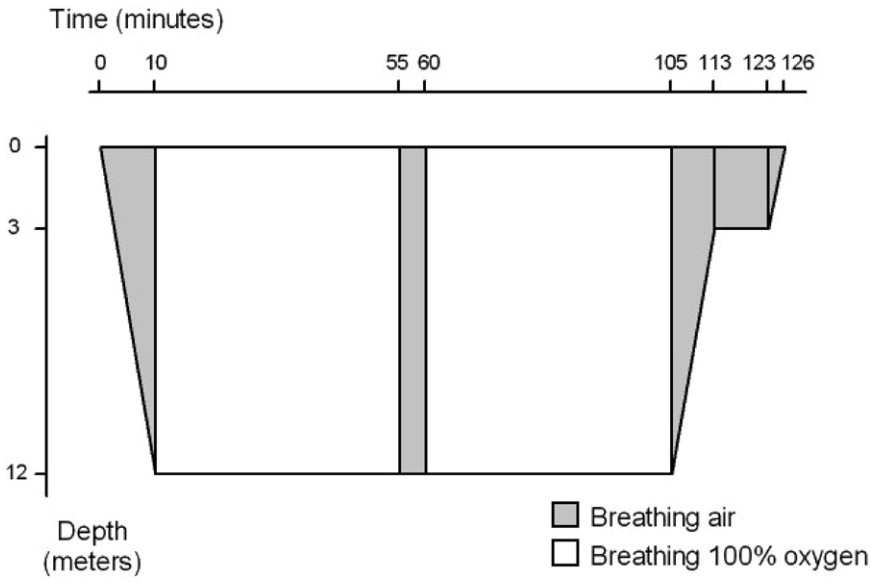

FIGURE 1. Treatment profile.

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quested, such as radiotherapy dose (Table 1). This is due to the patient files being incomplete across organizations, oncology units using separate computer systems from the other referring hospitals, and the expense (financially and in time) of patient note reviews. In addition to these issues, it was impossible to include control groups because of funding issues. With this in mind, a repeated measures design was chosen for the study, providing some degree of internal control to the data collection. A randomized placebo-controlled trial is, of course, the gold standard methodology and minimal air compression is an effective blinding tool for patients enrolled in hyperbaric trials.[20] Multicenter studies with this patient cohort looking at the effect of HBO_2 and surgery are underway using this methodology. However, there is considerable operational expense, and with the addition of ethical and logistical considerations, this can more than double the costs.

Table 2. MEDICAL OUTCOMES SHORT FORM 36 SCORES

	n	T1, Mean (SD)	T2, Mean (SD)	T1 vs T2
Physical functioning	18	39.9 (11.1)	40.2 (12.0)	0.3
Role—physical	18	28.4 (10.0)	32.0 (11.8)	3.6
Bodily pain	18	46.2 (10.4)	47.8 (10.7)	1.6
General health	18	39.3 (12.5)	44.7 (9.6)	5.4
Vitality	18	46.0 (10.4)	47.9 (11.1)	1.9
Social functioning	18	62.0 (24.8)	42.8 (12.4)*	−19.2
Role—emotional	18	23.5 (14.2)	32.5 (16.8)	9.0
Mental health	18	46.7 (12.0)	51.0 (10.5)	4.3

NOTE. A higher score indicates a better quality of life; therefore, a negative difference indicates a decline in quality of life.

Abbreviations: n, number of participants' data used in the calculation; SD, standard deviation; T1, before hyperbaric oxygen therapy; T2, after hyperbaric oxygen therapy.

*Significant at .01.

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Previous work by the present authors in patients with HNC undergoing HBO_2 perioperatively attributed improvements in QoL to the combination of HBO_2 and surgery.[16] That work was criticized for the risk of possible type I errors owing to the large amount of data being presented.[21] Some of the same scales were used in the present work and, therefore, to a limited extent the same criticism could be made. A Bonferroni correction could be used to correct for this. However, the Bonferroni correction is a very conservative measurement and would lead to an increased risk of type II errors (rejecting significances that are actually present).[22] Therefore, a more conservative level of significance ($P \leq .01$) was chosen. Power calculations performed on the data collected suggest that a sample size of 50 patients completing questionnaires before and after HBO_2 would allow a greater understanding of the effect of treatment and patient variables, including age and gender. Larger numbers would be required to investigate the influence of factors such as smoking/alcohol status and body mass index. These latter factors may be of interest because they have previously been shown to influence the onset of ORN.[23-25]

Table 3. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER CORE 30 QUESTIONNAIRE DATA

	n	T1, Mean (SD)	T2, Mean (SD)	T1 vs T2
Global health status/QoL*	18	57.9 (14.7)	69.6 (12.5)	11.7
Physical functioning*	18	72.2 (17.9)	75.7 (19.0)	3.5
Role functioning*	18	70.4 (29.5)	64.3 (32.0)	−6.1
Emotional functioning*	18	63.4 (21.2)	81.0 (18.6)‡	17.6
Cognitive functioning*	18	61.1 (22.9)	75.6 (22.2)	14.5
Fatigue†	18	40.1 (21.9)	41.8 (23.2)	1.7
Nausea and vomiting†	18	8.3 (11.8)	3.6 (7.1)	−4.7
Pain†	18	25.9 (24.4)	25.0 (23.3)	0.9
Dyspnea†	18	33.3 (25.6)	23.8 (30.5)	−9.5
Insomnia†	18	50.0 (34.8)	31.0 (33.2)‡	−19.0
Appetite loss†	18	29.6 (36.0)	15.4 (32.2)	−14.2
Constipation†	18	18.5 (28.6)	14.3 (25.2)	−4.2
Diarrhea†	18	0.0 (0.0)	2.4 (8.9)	2.4
Financial impact†	18	27.8 (30.8)	14.3 (21.5)	−13.5

Abbreviations: n, number of participants' data used in the calculation; QoL, quality of life; SD, standard deviation; T1, before hyperbaric oxygen therapy; T2, after hyperbaric oxygen therapy.

*Higher score indicates better function.

†Higher score indicates more symptoms.

‡Significant at .01.

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Many facets of QoL approach normal levels after the initial decreases around the time of treatment.[3] In the present research, the mechanism of the referral and treatment process prevented the authors from assessing the longitudinal stability of QoL measurements in this patient group; however, the mean average assessment of the patients was 55 months (4 yr 7 mo) after treatment. Chandu et al[3] suggested that short-term morbidity can be generally stable after 1 year, and nearing precancer levels by 3 years. It is reasonable to assume the QoL in these patients to be stable before HBO_2 and, hence, that the changes found in this study are due to HBO_2 and the experiences they had while at the hyperbaric medical center undergoing treatment.

The SF-36 is often used in medical trials as a standalone measurement and has been shown to be reliable and valid in a clinical setting.[17,26] In a previous study on HBO_2 and a similar patient group, the SF-36 failed to identify any changes in QoL.[16] With the present patient group, the SF-36 indicated a decrease in reported "social functioning." This most likely was because the patients spent an extended period away from home and, therefore, their family and social activities. The same explanation can be given about the decrease in sexuality identified in the EORTC QLQ-HN35 (although not significant). The other SF-36 domains identified positive trends (Tables 2, 4), suggesting that there is a significant positive effect on the patients being in a group of people who have experienced a similar illness, treatments, and side effects. Anecdotal reports from patients at the Hyperbaric Medical Centre in Plymouth suggest that improvements in mouth opening and the physical sensations relating to this change make talking more comfortable. A qualitative study may provide a greater insight into the specifics of the positive effects, but the authors postulate that this improved ability to talk to and see others coping with similar issues gives patients the resources to be more emotionally and mentally able. There are limitations to this hypothesis. The Hyperbaric Medical Centre does not treat only patients with ORN after treatment for HNC; they also treat conditions such as diabetic foot ulcers. This variation in patient cohort means that there were members of the study group who received HBO_2 but

Table 4. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER HEAD AND NECK 35 QUESTIONNAIRE DATA

	n	T1, Mean (SD)	T2, Mean (SD)	T1 vs T2
Pain	18	35.3 (25.4)	32.1 (20.9)	−3.2
Swallowing	18	27.9 (20.6)	19.4 (17.9)	−8.5
Senses problem	18	40.2 (36.8)	35.9 (41.9)	−4.3
Speech problems	18	28.8 (19.7)	22.2 (21.8)	−6.6
Trouble with social eating	18	52.3 (23.5)	30.8 (26.4)*	−21.5
Trouble with social contact	18	24.7 (22.8)	22.6 (26.2)	−2.1
Less sexuality	18	52.0 (41.6)	65.3 (33.7)	13.3
Teeth	18	48.9 (43.4)	22.2 (30.0)*	−26.7
Opening mouth	18	74.5 (32.3)	57.1 (35.6)	−17.4
Dry mouth	18	58.8 (41.7)	51.3 (44.3)	−7.5
Sticky saliva	18	49.0 (41.0)	56.6 (34.4)	7.6
Coughing	18	31.4 (18.5)	25.6 (30.9)	−5.8
Felt ill	18	19.6 (20.6)	15.4 (22.0)	−4.2
Pain killers	18	55.6 (51.1)	57.1 (51.4)	1.5
Nutritional supplements	18	44.4 (51.1)	28.6 (46.9)	−15.8
Feeding tube	18	5.6 (23.6)	0.0 (0.0)	−5.6
Weight loss	18	16.7 (38.3)	0.0 (0.0)	−16.7
Weight gain	18	11.1 (32.3)	28.6 (46.9)	17.5

NOTE. For all items and scales, high scores indicate more problems; therefore, a negative difference indicates an improvement in quality of life.

Abbreviations: n, number of participants' data used in the calculation; SD, standard deviation; T1, before hyperbaric oxygen therapy; T2, after hyperbaric oxygen therapy.

*Significant at .01.

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did not have other patients with HNC with whom to talk and socialize. It was also the case that some patients with HNC did not engage with their patient peers. This means that the delivery of the HBO_2 was carefully controlled and can be assessed and evaluated, but socialization and its mechanism of action is more complex and the number of participants in this study is insufficient to be able to make any generalizable conclusions about its impact on QoL.

The EORTC QLQ-C30 is a well-developed, reliable, general QoL instrument for patients with cancer. Although this questionnaire has cancer specific subscales, in the present case, the QLQ-HN35 and the global element (QLQ-C30) showed significant improvement in the ORN group. The decrease in "insomnia" may be explained by the improvement in "emotional functioning" (Table 3). Because insomnia is common in this patient group with psychiatric morbidity, the authors considered there may well be a link between these improvements.[27] This finding suggests that, even after completion of treatment, patients with cancer can benefit from group interaction and support.

The EORTC QLQ-HN35, like the other scales, produced data showing a positive trend for QoL across most domains. However, only 2 significant differences were "social eating" and "teeth" ($P \leq .01$ for the 2 comparisons; Table 4). The improvement in "social eating" may be explained by the informal patient interaction that occurs at the hyperbaric unit. Patients can talk about their condition and the problems that are affecting them, often leading to an exchange of problem solving, which includes attitudes toward eating in public and an increase in self-confidence. The change in relation to "teeth" cannot be explained by psychological factors. The domain within the EORTC QLQ-HN35 is a single item: Have you had problems with your teeth? After HBO_2 the patients reported significantly fewer problems than before treatment. No surgical or dental interventions had taken place, so the changes confidently can be attributed to HBO_2. This change correlates with the clinicians' reported stabilization of ORN.

HBO_2 is not generally used as the sole medical treatment of ORN. In fact, the use of HBO_2 in combination with surgery as a medical intervention for all types of ORN is still controversial.[28-33] However, the findings of this study support the thesis that HBO_2 has a positive physiologic and psychological impact on some factors for this patient group.

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