Int. J. Oral Maxillofac. Surg. 2014; 43: 107–112
http://dx.doi.org/10.1016/j.ijom.2013.07.006, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Pathology
Clinical Paper

Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa

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J. Svalestad, E. Thorsen, G. Vaagbø, S. Hellem: Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa. Int. J. Oral Maxillofac. Surg. 2014; 43: 107–112. © 2013 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. The aim of this study was to evaluate the effect of hyperbaric oxygen therapy (HBOT) on vascular function and tissue oxygenation in irradiated facial skin and gingival mucosa. Twenty-two patients, aged 51–90 years, were randomly allocated to a treatment or control group. All had a history of radiotherapy (50–70 Gy) to the orofacial region 2–20 years previously. Skin and mucosal perfusion were recorded with laser Doppler flowmetry (LDF). Tissue oxygenation was recorded by transcutaneous oximetry ($TcPO_2$). Measurements were taken before HBOT and 3 and 6 months after a mean of 28 HBOT sessions (partial pressure of oxygen of 240 kPa for 90 min). For control subjects, measurements were taken on two occasions 6 months apart. After HBOT, blood flow in mucosa and skin after heat provocation increased significantly ($P < 0.05$). $TcPO_2$ increased significantly in the irradiated cheek ($P < 0.05$), but not at reference points outside the field of radiation. There were no differences between the 3- and 6-month follow-ups. In the control group, no significant changes in LDF or $TcPO_2$ were observed. It is concluded that oxygenation and vascular capacity in irradiated facial skin and gingival mucosa are increased by HBOT. The effects persist for at least 6 months.

Keywords: angiogenesis; blood flow; laser Doppler flowmetry; microcirculation; radiotherapy; transcutaneous oximetry.

Accepted for publication 4 July 2013
Available online 6 August 2013

Radiotherapy is an established treatment modality in the management of head and neck cancer, either used alone or as an adjunct to surgery and/or chemotherapy. Despite advances in dose planning, some healthy tissue will still be included in the field of radiation and sustain injury. During the intensive phase of radiotherapy, tissue injury is evident clinically as mucositis and dermatitis, caused by a depletion of proliferating cells and by inflammatory responses[1]. These acute side effects eventually resolve during the post-irradiation period.

The acute vascular effects include hyperemia and increased vascular permeability, with perivascular fibrin leakage. Over time, the vessels continue to deteriorate, with obliterative endarteritis, thrombosis, and reduced neovascularization, eventually leading to hypovascularity, hypoxia, and fibrosis of the tissue[2]. These effects may remain subclinical for many years, but lead to atrophy, contracture, and potentially debilitating necrosis of soft tissue and bone.

Hyperbaric oxygen therapy (HBOT) is used to induce angiogenesis and increase oxygen tension to improve wound healing in irradiated tissue. Breathing oxygen at an

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increased pressure allows more oxygen to be dissolved in blood plasma. This is thought to induce a steep oxygen gradient between hypoxic, irradiated tissue and surrounding normal tissue, thereby stimulating angiogenesis mediated by macrophages[3]. Recent studies have provided further insight into the mechanisms underlying the effect of HBOT on irradiated tissue: HBOT increases levels of growth factors, such as vascular endothelial growth factor (VEGF)[4], and stimulates vasculogenic stem cell mobilization from the bone marrow in response to oxidative stress[5].

The use of HBOT has been supported by animal studies[2], tissue oxygen studies[6], and randomized clinical trials in various tissues[7–9]. However, the level of evidence is still considered relatively poor[10], and conflicting clinical results are reported in the literature[11]. Furthermore, Rudolph et al. reported normal oxygen tension levels in irradiated skin long after radiotherapy[12]. This contradicts the concept of irradiated tissue as a chronic hypoxic wound; hence there has been less focus on research into the effects of radiation on vascular tissue[13].

Thus there is a need for further investigation of the role of microcirculation and the effect of HBOT on late radiation-induced tissue injury. Doll et al. applied laser Doppler flowmetry to assess cutaneous microvascular tissue after radiation[14]. This method is now available for clinical application and has been evaluated for use in gingival mucosa[15]. Furthermore, provocation testing using oxygen breathing can be used for transcutaneous oxygen measurements[16] and may yield further insight into microvascular function in irradiated tissue. To the best of our knowledge, there are no previously published reports of functional assessment of the effect of HBOT on microcirculation in irradiated tissue.

The aim of the present study was to test the null hypothesis of no effect of HBOT on vascular function and oxygen tension in irradiated facial skin and gingival mucosa.

Materials and methods

Ethics

Participation in the study was based on the written informed consent of each subject. The study protocol was approved by the regional committee for medical research ethics and the privacy ombudsman for research. The study was conducted in accordance with the Declaration of Helsinki.

Subjects

The subjects comprised 22 patients, 15 men and seven women, age range 51–90 years. Patients formerly treated for head and neck cancer and referred to the Hyperbaric Medical Unit at Haukeland University Hospital, Bergen, Norway, were consecutively recruited and allocated to a treatment group ($n = 14$) or a control group ($n = 8$). Group assignment was made after enrolment using a predetermined randomized allocation sequence. The inclusion criterion was a history of radiotherapy $\geq$50 Gy to an area including the oral cavity. Exclusion criteria were unwillingness to receive HBOT, previous treatment with HBOT, active malignant disease or other medical conditions precluding HBOT, and inability to attend the follow-up regimen. Fifty-four patients were invited to participate, giving a participation rate of 41%. Patients were not asked to give any reason for non-participation. The patient characteristics, radiation dose, and time elapsing since radiotherapy are summarized in Table 1. Indications for HBOT were clinical osteoradionecrosis, xerostomia, or as a prophylactic measure before tooth extraction or other surgical procedures. Radiotherapy had been given by fractionated three-dimensional conformal radiotherapy with multiple fields. Dose-fractionation was 2 Gy per day, 5 days per week. The individual dose plans were evaluated to identify the areas of maximal irradiation.

Table 1. Patient characteristics.

Male/female	HBO group ($n = 14$)		Controls ($n = 8$)	
	9/5		6/2	
	Mean	Range	Mean	Range
Age, years	65	51–90	60	53–73
Blood pressure, mmHg				
Systolic	133	104–150	128	108–154
Diastolic	74	63–91	76	61–93
Radiation dose, Gy	66	50–70	65	50–70
Time since radiation, years	6	2–20	4	2–6

HBO, hyperbaric oxygen.

Hyperbaric oxygen therapy (HBOT)

Patients received HBO treatment once daily, 5 days a week, for an average of 28 days. The patients were compressed with oxygen in a monoplace hyperbaric chamber to a pressure of 240 kPa within 10–15 min. Oxygen was breathed at this pressure for 90 min, in three cycles of 30 min, with breathing of compressed air from an oronasal mask for 5 min between cycles. They were decompressed to atmospheric pressure in 7–10 min.

Laser Doppler flowmetry (LDF)

LDF is based on the frequency shift of backscattered laser light from moving objects, to assess the flow of blood cells in superficial vessels[17]. The magnitude of the shift and the intensity of the backscattering are processed, yielding information on perfusion, calculated as the average speed multiplied by the concentration of blood cells in the tissue layers beneath the probe. The instruments were calibrated using a latex suspension, in accordance with the manufacturer's instructions.

Transcutaneous oximetry ($TcPO_2$)

The principle underlying this method of measurement is that temperature-induced vasodilation increases oxygen availability to levels greater than the metabolic demand of local tissue. Oxygen then diffuses from skin capillaries through dermis and epidermis to the sensor. An electrochemical reaction between diffused O_2 molecules and a cathode in the $TcPO_2$ sensor produces an electrical current proportional to the amount of consumed oxygen.

Gingival and skin perfusion measurements

Gingival perfusion was recorded on the buccal gingiva within the field of maximum radiation dose, using a custom-made, tooth-supported acrylic splint. A custom-designed gingival thermostatic multiprobe (Perimed AB, Järfälla, Sweden) was secured by a probe holder fixed to the acrylic splint. Measurements were preferably taken at an edentulous gingival site. In dentate sites, the probe was placed at least 5 mm away from the gingival sulcus or dental papilla, in order to avoid

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