Hyperbaric Oxygen Therapy and Mandibular Osteoradionecrosis: A Retrospective Study and Analysis of Treatment Outcomes

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Abstract

Background: *Hyperbaric oxygen (HBO) therapy is recognized as an adjunctive treatment for osteoradionecrosis (ORN). It may also be used prophylactically in patients who require dental extractions and are at high risk for developing ORN. This article reviews the treatment outcomes of patients treated with HBO therapy at the Toronto General Hospital from 1985 to 1997.*

Materials and Methods: *A total of 297 charts of patients treated with HBO were reviewed. Criteria assessed included age of patient, gender, original diagnosis, radiation dose, time between radiation treatment and onset of ORN, presence or absence of fracture, orocutaneous fistula, pain, history of a precipitating event triggering ORN, medical status, HBO therapy (total oxygen time, number of dives), method of treatment of ORN and follow-up period. Minimum patient follow-up time for inclusion in the study was 6 months.*

Results: *Adequate information to meet the inclusion criteria was obtained for 75 patients. Group A (51 patients) had been treated for overt ORN with HBO alone, HBO with sequestrectomy, or HBO with sequestrectomy and reconstruction. Group B (24 patients at risk for developing ORN) had been treated with HBO prophylactically for dental extractions. In group A, only 3 patients (5.9%) failed to show improvement. In group B, only one patient (4.2%) had complications during healing.*

Conclusions: *Encouraging results were achieved when HBO was used in the 2 groups described above. This paper supports existing literature on the potential benefit of HBO as a prophylactic agent and adjunctive treatment of ORN.*

MeSH Key Words: *hyperbaric oxygenation; mandibular diseases/therapy; osteoradionecrosis/therapy*

© J Can Dent Assoc 2001; 67:384
This article has been peer reviewed.

Osteoradionecrosis (ORN) is a dreaded complication of the use of radiation therapy in the treatment of head and neck cancer. ORN consists of necrotic soft tissue and bone that fail to heal spontaneously and do not respond to local care over a period of 6 months.[1,2] Radiation induces tissue hypoxia in normal cells, resulting in an imbalance where cell death and collagen lysis exceed the homeostatic mechanisms of cell replacement and collagen synthesis. This results in a wound that will not heal, in which the metabolic demands exceed the oxygen and vascular supply. Cell and host susceptibility to such radiation damage is not uniform and may vary among individual patients.[1]

Clinical manifestations of ORN may include pain, orocutaneous fistula, exposed necrotic bone, pathologic fracture, and suppuration.[3-5] ORN is more commonly seen in the mandible than in the maxilla due to the relatively decreased vascularity and increased bone density of the mandible. In addition, the mandible often receives a greater dose of radiation than the maxilla.

Contributing factors to the development of ORN are well known: dental trauma, the premorbid state of the

Figure 1: *Multiplace hyperbaric oxygen chamber capable of housing several patients and a therapist during a dive.*

Figure 2: *Two side-by-side monoplace chambers. The clear glass allows patients to watch television or videos and helps assuage fears of confinement in claustrophobic patients.*

dentition, tumour location, radiation dosage, delivery and fractionation, elapsed time since radiation, nutrition, alcohol and tobacco use, and concomitant surgery and chemotherapy.[6-8] Clinically there are 3 types of ORN. Type I is trauma-induced ORN which occurs when radiation or surgical wounding are coupled closely together. The most common is Type II, also trauma-induced ORN, which occurs years after radiation therapy. Type III or spontaneous ORN can occur anytime after radiotherapy but commonly occurs 6 months to 2 years following radiotherapy, without any obvious preceding surgical or traumatic event.[9,10]

Over the years, ORN has been treated by numerous methods with less than ideal results and variable success rates.[3] Although still considered controversial by some, hyperbaric oxygen (HBO) therapy used as an adjunctive treatment for ORN has been associated with improved success rates.[4,5,7,11-14] There are also reports that HBO has provided beneficial results when used prophylactically for the extraction of teeth in patients deemed to be at risk for developing ORN,[15-17] although this success is disputed by some.[6] HBO therapy is a treatment modality which provides an increased oxygen tension at the tissue level to promote healing, especially in wounds with a compromised vasculature. This is accomplished by placing a patient in a pressure-tolerant chamber, either alone (in a monoplace chamber), or with more than one patient or a therapist (in a multiple chamber). The chamber is pressurized at 2.4 atmospheres absolute and, depending on the protocol, patients remain inside for one hour.

The purpose of this study was to assess treatment outcomes of HBO therapy with respect to ORN of the mandible at the Toronto General Hospital. Both the adjunctive protocol for the treatment of overt ORN and the prophylactic protocol in patients who were at risk for developing ORN and requiring dental extractions were evaluated. The patients' premorbid medical status was also evaluated to determine whether it had an impact on treatment success.

Materials and Methods

Charts were analyzed of all patients who were treated for mandibular ORN with HBO therapy at the Toronto General Hospital from 1985 to June 1997. Patients' charts were also reviewed if they had HBO treatment prophylactically for the extraction of teeth. Medical, HBO, oral and maxillofacial surgery, and otolaryngology charts were reviewed, for a total of 297 charts. Phone calls were made to referring surgeons and dentists to obtain or clarify any information as needed. The criteria assessed included age of patient, gender, original diagnosis, radiation dose, time between radiation treatment and onset of ORN, presence or absence of fracture, orocutaneous fistula, pain, history of a precipitating event which triggered the ORN, medical status, HBO therapy (total oxygen time, number of dives), method of treatment of ORN, and follow-up period. The minimum patient follow-up time for inclusion in the study

Table 1 **Original diagnosis and anatomical sites in 51 patients with overt ORN**

Anatomical site	No. of patients
Tongue[a]	15
Floor of mouth[a]	8
Palate[a]	5
Oropharynx/pharynx[a]	5
Buccal/lingual mucosa[a]	4
Nose/nasopharynx[a]	3
Oral cavity[a]	3
Retromolar trigone[a]	2
Mandible[a]	2
Lymphoma	2
Actinomycotic infection	1
Submandibular gland tumour	1

[a]*squamous cell carcinoma*

Table 2 **Treatment outcomes of HBO used for overt ORN**

Treatment	No. of patients	Success	Improvement	No improvement
HBO alone	19	7	11	1
HBO and sequestrectomy	20	18	1	1
HBO and resection	12	11	0	1

was 6 months. Patients were deemed medically compromised if they had peripheral vascular disease or diabetes.

HBO treatments were delivered at the Hyperbaric Oxygen Unit at the Toronto General Hospital. Patients were treated daily at 2.4 atmospheres absolute (ATA) for one hour in a multiplace or monoplace chamber (Figs. 1 and 2). The Marx protocol[1,18] was used as a guide for the number of treatment dives needed. However, due to variations in patient compliance, patient tolerance to treatment, and response of the lesion, some deviation from the protocol occurred in certain cases. Patients treated for overt ORN had HBO therapy with total oxygen time ranging from 1,730 to 5,940 minutes (20 to 40 preoperative dives and 14 to 20 postoperative dives). HBO therapy was deemed successful if all of the following 3 criteria were met: no bone exposure, closure of fistula (if originally present), and an asymptomatic status. "Improvement" was assigned to patients in whom one or 2 of these criteria were met. If none of the above criteria were met, a patient was deemed to be "not improved."

Patients who were at risk for developing ORN and had tooth extractions received HBO therapy with total oxygen time ranging from 1,980 to 3,390 minutes (6 to 21 preoperative dives and 2 to 24 postoperative dives). These patients were surveyed for postoperative complications.

Results

After reviewing the records, adequate information to meet the inclusion criteria of this study was obtained for 75 patients. Two groups emerged from this sample: group A, which consisted of 51 patients with overt ORN who were treated with HBO and various surgical treatments, and group B, which consisted of 24 patients at risk for developing ORN who were treated with HBO prophylactically for dental extractions.

Group A

This group consisted of 29 men and 22 women ranging in age from 37 to 88 years (mean age of 62.2 years). Their original diagnoses are outlined in Table 1. Estimated radiation dosages ranged from 1,590 centigrays (cGy) (for a patient with an actinomycotic infection) to 8,770 cGy (iridium implant and external beam, for a patient with recurrent floor of mouth cancer). Unfortunately, no further details about the radiation dosages were retrievable. The majority of patients (70.5%) received between 5,000 cGy and 6,060 cGy. ORN occurred anywhere from 4 months to 60 months after the conclusion of the radiation treatment. Patients were seen for follow-up for 6 months to 9 years after completion of HBO therapy. The mean follow-up time was 1.8 years. ORN was caused by trauma in 34 patients (66.7%). This was further qualified as follows: 30 patients had dental extractions, 2 patients had denture-related trauma, and 2 patients had surgery due to failed radiation. In 17 patients (33.3%) ORN occurred spontaneously. With regard to the patients' medical status, only 2 patients had peripheral vascular disease and one patient had insulin-dependent diabetes.

The final treatment of ORN depended on the severity of the condition. Patients in this study were treated with HBO alone (19 patients), HBO and sequestrectomy (20 patients), or HBO and mandibular resection and reconstruction (12 patients). Outcomes of treatment are illustrated in Table 2.

Group B

Group B consisted of 13 men and 11 women ranging in age from 35 to 78 years. The mean age was 61 years. Eight teeth were removed in one patient, half of which were in the field of radiation, and 5 were extracted in another (3 teeth were in the line of radiation). Of the remaining 41 extracted teeth, 37 were within the field of radiation. Three teeth were removed in one patient, 2 teeth were extracted in 17 patients, and one tooth was extracted in 4 patients. A total of 54 mandibular teeth were extracted in all. Eighteen required judicious elevation of a flap and minor bone removal; all of these teeth were within the field of radiation. The remaining 36 were nonsurgical extractions. These patients had primary tumours in the following anatomic sites: tongue (5 patients), floor of mouth (4), buccal mucosa (2), nose/nasopharynx (4), parotid (3), larynx (3), lip (1), oropharynx (1), and alveolus (1). Radiation dosages ranged from 3,000 cGy to 13,000 cGy; 12 of the 22 patients received radiation greater than or equal to 6,000 cGy. The very high dose of 13,000 cGy was a dose acquired at 2 different times. The patient was first irradiated postsurgically for adenoid cystic carcinoma of the parotid and then later for a recurrence. Time between radiation and extractions for the patients in this group ranged from 8 months to 22 years. Unfortunately, no further details of the radiation treatment were obtainable. None of the patients were medically compromised. The follow-up time period ranged from 6 months to 2.3 years, with a

Table 3 **Treatment outcomes in ORN prophylaxis group**

Treatment	Extractions	Complications
Nonsurgical	36	1
Surgical	18	0

mean of 10.3 months. All of the patients except one had unremarkable postoperative healing. In that patient, however, a dry socket occurred in a nonsurgical extraction site. This problem did not progress to ORN but merely prolonged healing. Treatment outcomes are illustrated in Table 3.

Discussion

The pathophysiology of ORN is best illustrated by the "3 H" principle which describes the effect of radiation on tissue as presented in the landmark article by Marx.[9] Radiation leads to progressively hypocellular, hypovascular and hypoxic tissues. This impedes the replacement of connective tissues and cells as part of tissue turnover in normal homeostasis and in wound healing. Breakdown of tissues can thus ensue with or without trauma. ORN is, therefore, a problem of impaired and inadequate tissue turnover and wound healing.

HBO improves tissue healing by increasing the oxygen gradient in irradiated tissues. In normal nonirradiated wounds, there is a central area of tissue injury surrounded by tissue with normal perfusion, setting up a steep oxygen gradient across the wound. Such gradients have been shown to be the physical–chemotactic factor attracting macrophages to a wound.[19,20] Lactate, iron and steep oxygen gradients stimulate macrophage-derived angiogenesis factor and macrophage-derived growth factor, which in turn promote capillary budding and collagen synthesis in wounds.[19] However, in wounds with radiation tissue injury, which inevitably results in diffuse damage, only shallow oxygen gradients are created. The stimulus for fibroplasia and angiogenesis is therefore lacking. HBO restores the steep oxygen gradient needed for wound healing.[19-21] Many authors have reported on the positive tissue effects of HBO therapy.[10,22-24]

The results of this study suggest that HBO may be beneficial as an adjunctive treatment for patients with overt ORN and for prophylactic use for dental extractions in patients at risk for developing ORN. When HBO was used as the sole treatment for patients with overt ORN, success or improvement occurred in 94.7% of patients. For patients treated with HBO and sequestrectomy, 95% either improved or were successful with their respective treatment. For patients treated with HBO and resection and reconstruction, 91.7% had successful outcomes. Only one patient failed treatment for each of these therapies. Maier and others,[25] however, found that postoperative HBO treatments together with surgical treatments yielded only a 65% success rate in a group of 20 patients.

Higher doses of radiation (> 6,000 cGy) and the presence of fracture or orocutaneous fistula or both correlated with the need for extensive treatment with resection and reconstruction. Maxymiw and others[6] stress the importance of dose per fraction as well as the estimated alveolar bone absorbed radiation dose. They point out that the prescribed tumour dose of radiation does not necessarily equal the absorbed bone dose. Unfortunately, the data in the present study do not lend themselves to a radiation dose analysis of such sophistication.

In 2 of the 3 treatment therapies, HBO served as an adjunctive treatment, whereas in some patients, HBO alone was therapeutic. In a retrospective review by McKenzie and others,[5] the efficacy of HBO in the management of 26 patients with ORN was assessed. Surgery was performed in 18/26 patients in addition to HBO therapy. Persistent mucosal and cutaneous coverage occurred in 18/26 patients, 13/26 patients met strict criteria for resolution, and 21/26 had improved post-HBO therapy. The longest follow-up was 14 years. The authors point out the highly variable clinical course of ORN. Selection of treatment must bear this in mind. "Treatment must always be individualized but the combination of HBO, other conservative management, and surgery will optimize treatment results in many patients. HBO with or without surgery appears to be an effective adjunct in the treatment of post radiation necrosis."[5] A second study by Epstein and others[26] assessed these 26 patients for an additional 5 years of follow-up. Of these 26 patients, 20 were evaluated and 2/20 experienced a second episode of ORN. Five patients continued to demonstrate chronic persisting postradiation ORN. In 12 patients, the ORN remained resolved and 2 patients experienced improvement.

In the present study, when HBO was used prophylactically in patients requiring dental extractions, the authors obtained encouraging results. In this group, 18 of the 54 extractions required surgical removal; 98.1% of the total number healed uneventfully. Universal agreement regarding the prophylactic use of HBO for dental extractions does not exist.[6,27,28] The results of this study have added to those in agreement with its prophylactic use.[17,29]

Unfortunately, this study lacks a control group for comparison with patients having had dental extractions without the use of HBO. However, studies exist solely examining extractions without the use of HBO. Maxymiw and others[6] examined the incidence of ORN after dental extractions without the use of HBO. Low epinephrine or epinephrine-free, nonlidocaine local anesthetic was used as well as pre- and postoperative prophylactic antibiotic coverage. A sample of 196 teeth were within the field of radiation; 73 of these were maxillary teeth. No cases of ORN occurred. The authors state that "an atraumatic surgical technique that avoided periosteal elevation was employed."[6] Their zero incidence of ORN is, therefore, for these specific types of extractions. In the present study, surgical extractions were performed in some cases.

Epstein and others[30] reported on the clinical experience of 627 dental extractions in 146 patients at risk of developing ORN. Of the 627 extractions, 454 occurred before radiation, 137 after, and 36 during radiation treatment. Prophylactic antibiotic coverage was given to the patients, and primary closure of the surgical sites was performed. Eight patients developed ORN, yielding an incidence of 5.6%. Three of these 8 cases occurred in patients whose teeth were extracted postradiation; 52 patients had extractions after radiotherapy. Beumer and others[31] reported their experiences involving 72 extractions. When single tooth extractions were performed, primary closure was rarely obtained. However, when multiple teeth were removed mucoperiosteal flaps were raised and radical alveolectomies were performed as needed to achieve primary closure. The incidence of ORN was 22% with the majority of cases occurring in the mandible.

The only controlled randomized study in the literature is that of Marx and others.[29] They compared the use of HBO versus antibiotic coverage in the prevention of ORN when extractions were performed in patients who had undergone radiation treatment. Both groups had 37 patients in each of them. In the group that received the antibiotic prophylaxis, 11/37 patients developed ORN. In the group of patients who only received HBO dives, only 2/37 patients developed ORN.

In the present study, the Marx protocol could not be strictly adhered to. There were compliance variations in some patients in both treatment groups. Perhaps the total oxygen exposure time is a key factor in some patients rather than the actual number of dives or the sequence of oxygen delivery. There may also be individual, variable susceptibility to treatment that may affect treatment outcome.

Only 3 patients were deemed medically compromised in this study (all in group A). No effect of their medical condition on treatment outcome could be detected. Given the small sample size, however, no definitive conclusions can be made.

Future research is necessary with multicentred, blinded, randomized, and prospective trials comparing overt ORN treatment with HBO used alone, with HBO used in conjunction with sequestrectomy or resection, and with surgery alone. A similar approach is necessary comparing extractions with and without HBO prophylaxis in individuals at risk for developing ORN. Given the expensive labour-intensive nature of HBO treatment compared to the potential tremendous cost of treating overt ORN, such information would be most valuable for future decision making and policy planning. ◆

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The authors have no declared financial interest in any company manufacturing the types of products mentioned in this article.

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