The Role of Hyperbaric Oxygen Therapy (HBOT) in Preventing Osteoradionecrosis: Interim Results from a Prospective Clinical Trial

ISOO Parallel Session Saturday, June 30, 2018 Vienna, Austria Dr. Allan Hovan, Department Head Program in Oral Oncology/Dentistry, British Columbia C<u>ancer (Vancouver)</u>

Outline of Presentation

The Clinical Problem (ORN)

• HBO in Prevention: Does it Work?

Designing a Study to Find Out

Interim Results: Emerging Questions

The Clinical Problem (ORN)



Historical Definition of ORN

A non-healing mucosal or skin opening with underlying exposed devitalized bone in area of previous high-dose radiotherapy



Prevalence of ORN

Table 1. Weighted prevalence from 31 studies.⁴

Modality	Prevalence
Conventional RT	7.4%
Intensity Modulated RT	5.2%
Chemo-radiotherapy	6.8%
Brachytherapy	5.3%

Adapted from Peterson, Hovan et al, 2010



Conventional



IMRT



Conventional

IMRT

Risk Factors for ORN

- Exposure > 6000 cGy ^{5, 9, 10, 13}
- Posterior mandible exposed ¹¹
- Poor dentition and oral hygiene ¹²
 - Poor nutrition ¹⁴
 - Smoking ⁶
- Ill-fitting prosthesis causing chronic trauma ¹¹
 - Post-RT extraction ¹³

- 5) Reuthers et al, Int J Oral Maxillofac Surg, 2003.
- 6) Freiberger et al, Int J Radiat Oncol Biol Phys, 2009.
- 9) Katsura et al, Oral Surg Oral Med Oral Pathol, 2008.
- 10) Thorn et al, J Oral Maxillofac Surg, 2000.

- 11) Kluth et al, J Prosth Dent, 1988.
- 12) Murray et al, Oral Surg Oral Med Oral Path, 1980.
- 13) Schwartz & Kagan, Am J Clin Onc, 2002.
- 14) Teng et al, Current Opinion, Otolaryng Head Neck Surg, 2005.

The Purported Solution - HBO What is HBO?

 Patient breathes oxygen at a pressure ~ 2.5X greater than normobaric pressure (1ATA) for a predetermined period of time

• Typical "dosing" is 2.4 ATA X 90 minutes

• Drug = Oxygen

Dosing Apparatus = Hyperbaric Chamber



ORN Treatment Protocol Details

 Prophylaxis when surgery is performed in radiated tissue without frank RN (eg. dental extractions, implant placement, etc.)

20/10

Established ORN (Marx or Miami protocol)

30/10

Rationale for Hyperbaric Oxygen Therapy



HBO increase blood-tissue oxygen gradient
 Fibroblast proliferation, angiogenesis, collagen formation^{1, 7}
 Bactericidal & bacteriostatic⁷

Marx, J Oral Maxillofac Surg, 1983.
 Marx & Johnson, Oral Surg Oral Med Oral Path, 1987.

Vancouver HBU Statistics # Treated 2016-2017 (23 months)

Delayed Radiation Injury	69
Problem Wounds	47
CO Poisoning	36
Decompression Sickness	25
Chronic Refractory Osteomyelitis	13
Sensori-Neural Hearing Loss	
Gas Embolus	
Necrotizing Soft Tissue Infections	7
Clostridial Myonecrosis	5
Compromised Flaps / Grafts	2
Severe Blood Loss Anemia	1

Peterson et al

Support Care Cancer (2010) 18: 1089-1098 Recommendations for Future Research

1. Are there specific valid predictors of ORN risk?

2. Is there a subset of patients at risk for ORN for whom HBO is/is not effective?

3. What is the role of "adjuvant preventive therapy" (including HBO)?

The Controversy: HBO for post-RT extractions?

For

Against

CLINICAL CONTROVERSIES IN ORAL AND MAXILLOFACIAL SURGERY: PART ONE

J Draf Mountaine Surg. 68.048 274, 1007

Management of Dental Extractions in Irradiated Jaws: A Protocol With Hyperbaric Oxygen Therapy

PAUL M. LAMBERT, DDS,* NANCY INTRIERE, DMD,† AND RALPH EICHSTAEDT, DDS‡

Dental management of patients who are about to receive, or who have completed a course of therapeutic radiation involving the jaws, remains a perpieting problem. The center of debate is whether to extract useth before radiation therapy or to manage them more conservatively and preserve the dentition to the greatest extent possible. The principal concern in this debate is how to minimize the risk of developing the most destructive complication associated with head and neck radiatione, onteoradionecrosis (ORN).

Tamoricidal levels of irradiation damage all tissues exposed. The accepted came of ORN is progressive obliterative endasteritis and fibrosis resulting in hypovascular, hypocellular, and hypoxic tissues that can necrose spontaneously or in response to trauma. The incidence of ORN after radiation is reported to be widely different in several studies, ranging between 2% and 85%.⁵⁴ The causal relationship between dental extractions and ORN has been discussed by several authors,⁴⁵⁰ Beamer et al¹¹ reported that the most common factors associated with ORN were postradiation extractions (26.5%), spontaneous hore exposure associated directly with the dentition secondary to dental disease (22.8%), and perendiation extractions (20.4%).

In an effort to prevent ORN, Marx et al¹² proposed prophylaxis with hyperbaric oxygen (HBO) before postradiation dental extractions. In a multicenter trial,

* Oral & Maxillofacial Surgeon and Chief, Dental Service, Veterans Allairs Medical Center, Depton OIL Associate Clinical Prefessor, Wright State University School of Medicine; Assistant Clinical Professor, Ohio State University College of Deniotry.

¹ Assistant Chief, Dental Service, Veterans Allairs Medical Center, New York, NY: Formorly, Staff Oral & Maxillofacial Surgeon, Veneme Allaire Medical Concern Dentase Cell. 74 patients were randomized to receive one of two treatments. One group received penicillin preoperatively and for 10 days after surgery. The second group received no antibiotics, but received HBO (20 sessions of 90 minutes each, breathing 100% humidified oxygen at 2.4 atmospheres absolute pressure before surgery and 10 sessions after surgery). Extractions were performed in the same manner in both groups using elevator mobilization and forceps delivery with minimal alveoloplasty and no attempt to achieve primary mucosal closure. The end point of the follow-up period was a "yes or no" clinical diagnosis of ORN defined as the presence of exposed bone in a study socket after 6 months. Three were 137 socket wounds in 37 patients in the antibiotic group and 156 sockets in 37 patients in the HBO group. In the antibiotic group, 31 sockets (22.6%) in 11 patients (29.9%) were positive for ORN, whereas only four sockets (2.6%) in two patients (5.4%) were positive for ORN in the HBO group.

Some clinicians believe that the high cost and limited availability of HBO precludes recommending its universal application for ORN prophylaxis.^{11,12} Maxymiw et al¹⁵ performed 449 extractions in 72 radiated (25 to 84 Gy) patients. All extractions were performed without HBO, and no ORN developed during the follow-ap period (median, 4.8 years).

In view of these findings, an important question remains with an unclear answer. Should unrestorable teeth be extracted before radiation therapy, after therapy with HBO prophylaxis' This article presents data from our own experience with adjunctive HBO for dental extractions and reviews the puthophysiology of

CLINICAL CONTROVERSIES IN ORAL AND MAXILLOFACIAL SURGERY: PART TWO

J Draf Manifelhet Surg 50,275-081, 1987

Management of Dental Extractions in Irradiated Jaws: A Protocol Without Hyperbaric Oxygen Therapy

LEWIS CLAYMAN, DMD, MD*

The absolute incidence and prevalence of osteoradionecrosis (ORN) of the jaws after radiation therapy (RT) for treatment of oral and oropharyngeal cancer are unknown. Since 1922, when Costard' reported the Fondation Curie's experience with ORN, one finds that it has been observed to occur in both deptalous and edentulous patients, either spontaneously or after wounding. In particular, ORN has been noted to occur after dental extractions performed shortly before or at any time after RT. Reviewing studies from the literature, most of which are retrospective, one finds an overall incidence of ORN of 11.8% before 1968 (Table 1) and 5.4% after that date (Table 2), by which time almost all radiation oncology units had embraced megavoltage or supervoltage therapy. These data were based only on the presence of ORN without subcateporization into dentalous, edentalous, spontaneous, or extraction related. Unfortunately, this risk, although highest during the first 4 to 12 months after RT, has been found to persist for the remainder of the patient's 116e. 1-10

The older concept of ORN developing consequent to a triad of RT above a critical dose, local trauma, and infections was articulated in 1928 by Watson and Scarborough¹⁰ with support by others.^{11,10} In the 1980s this concept was challenged by Marx,¹⁴¹ who suggested an alternate hypothesis that ORN resulted from radiation-induced, deficient cellular turnover and collagen synthesis in an hypoxic, hypovascular, and hypocellular environment in which tissue breakdown exceeded the repair capabilities of the wounded tissue.¹⁶

Because the presence of carious and periodostally compromised teeth in the irradiated mandible has long

been associated with ORN, controversy has existed regarding whether such teeth should be removed before or after RT, whether they should ever be removed. and, if they should be removed, when, by what technique, and by whom. Thirty years ago it was recognized that the maintenance of a healthy dentition was essential for the prevention of ORN. This required the willing participation of a dentist to assess and monitor the dentition and to remove teeth as necessary.16.17 All teeth that were grossly carious, periodontially hopeless, or had a poor prognosis for retention beyond 12 months⁸ were removed before RT.²⁶ with extractions after RT being avoided as much as possible.⁸ Fully embedded toeth were not removed.34.35 At the time of extraction, alveoloplasty with primary closure, the use of prooperative and postoperative antibiotics, and a 10-day wait before starting RT were recommended. Although the use of systemic antibiotics was well supported in the literature of this time, 1,11,19-21 a more recent article by Marciani and Ownboy²² reported excellent results both for pre-RT and post-RT extractions without using antibiotics. After the adoption of an organized plan to manage the dentition, and the use of high-energy radiation therapy in the years after 1968. the rate of ORN for extractions performed before RT fell to 4.4% (Table 3).

Most studies have reported a higher rate of ORN after dental extractions after RT than before it. However, in carefully evaluated patients who received aggressive preventive dental care and whose extractions were performed by experienced oral and maxillofacial surgeons, the five most recent studies have reported a prevalence of ORN of only 1.1% in 424 patients who had teeth removed after RT.²³³

Controversy: HBO for post-RT extractions?

For

Against

Marx trial (1985)
 74 patients for exo
 37 abx + HBO

Protocol	ORN Incidence
Abx + HBO	5.4%
Abx	29.9%

This remains the only randomized trial to-date to study this effect Systematic reviews: 1) Peterson, Hovan et al, 2010. • 1990-2008 (excludes Marx)

> "Use of prophylactic HBO therapy for prevention of ORN in post-RT extractions."

"Level of evidence III, recommendation grade C: no geteiolebine aposticate ancer, 2010

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This remains the only randomized trial to-date to study this effect Systematic reviews: 1) Peterson, Hovan et al, 2010. 2) Nabil & Samman, 2011. (19 studies)

Protocol	ORN Incidence
Abx + HBO	4%
Abx	6%

"Based on *weak evidence,* prophylactic HBO is effective in reducing ORN development after post-RT extractions."

Controversy: HBO for post-RT extractions?

For

Against

Marx trial (1985)
 74 patients for exo
 37 abx + HBO

Protocol	ORN Incidence	
Abx + HBO	5.4%	
Abx	29.9%	

Systematic reviews: 1) Peterson, Hovan et al, 2010. 2) Nabil & Samman, 2011. 3) Chuang, 2011. (14 studies) Protocol ORN Incidence Median

Abx + HBO0-11%4.1%Abx0-29.9%7.1%

This remains the only randomized trial to-date to study this effect

No statistically significant difference.

Is There Any Evidence to Support The Use of Prophylactic HBO Post-XRT?

Study Question:

Does Hyperbaric Oxygen Therapy (HBOT) reduce osteoradionecrosis (ORN) rates and improve Quality of Life (Q of L) in patients requiring oral surgical procedures following a course of high-dose head and neck radiation?

Objectives of Study:

1. To determine whether there is a lower rate and severity of ORN in head and neck radiotherapy patients who receive prophylactic HBOT prior to dental extractions.

2. To determine whether there is a difference in Quality of Life measures in subjects who received/did not receive HBOT

REB-Approved Study

 Prospectively enroll all H&N pts who received high-dose RT with or without concurrent chemotherapy who now require dental extractions to determine the prevalence of ORN when treated with or without prophylactic HBO.

• The HBO-treated patients will be from the BCCA who are routinely referred to the VGH HBU for prophylactic HBO

• The non-HBO control patients will be from the Northeast Cancer Centre in Sudbury Ontario who are not referred for prophylactic HBO



- Baseline assessments prior to oral surgery; each tooth assessed re (a) difficulty of extraction (b) effective dose
 - All patients given same pre-op and post-op medications; surgical technique standardized between centres
- Patients seen in first week post-extractions; then at 2 w, 1 m, 6m, 1 y and 2 y follow-ups
 - At each visit, assessed re +/- ORN; if present, ORN staged and managed
 - EORTC QLQ-30 and EORTC-43 (H&N) questionnaire applied at each visit

ORN Assessment Scales

Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

Grade 1: Asymptomatic; Radiographic findings only Grade 2: Symptomatic and Interfering with Function; Minimal Bone Removal Indicated Grade 3: Symptomatic and Interfering with Daily Life Activities; Operative or HBO Grade 4: Disabling

ORN Stage: Lyons et al. 2014

Stage 1: <2.5 cm; Asymptomatic Stage 2: >2.5 cm; Asymptomatic Stage 3: <2.5 cm; Symptomatic Stage 4: > 2.5 cm; Pathologic Fracture

Results to Date

Vancouver

Sudbury

 23 patients enrolled; 22 evaluable for QofL 45 patients enrolled to date; 30 evaluable for ORN; 27 evaluable for QofL

- 17 male; 6 female
- Age range 45-80 (62.2)

- 21 male; 9 female
- Age range 43-83 (61.1)

Results to Date

Vancouver

52 teeth extracted
(36 mandible; 16 maxilla)

- 1 case of ORN (Lyons); Stage 3; resolved with antibiotics and local debridement
- 2 cases of ORN (CTCAE); One Stage 1*; One Stage 2**

*=radiographic change only
**=fistula to bone; no bone exposure



- 55 teeth extracted (34 mandible; 21 maxilla)
- 1 case of ORN (Lyons); Stage 3; resolved with debridement and Pentoclo protocol
- 3 cases of ORN (CTCAE); 1 cases Stage 1*; 2 cases Stage 2**

*= radiographic change only
**=fistula to bone; no bone exposure

Quality of Life Data

 At each study visit, patients completed EORTC QLQ-C30 (general) and EORTC QLQ-H&N 43 (specific) and asked about any health and/ or medication changes

> Questions 29 and 30 (EORTC QLQ-30) 1-7 Lickert Scale (1=very poor; 7=excellent)

29. How would you rate your overall health this week?

30. How would you rate your overall quality of life this week?

Quality of Life Data

Vancouver

Question 29:

Baseline = 5.1

6 Months = 5.9

Question 30:

Baseline = 5.1 6 months = 6.0

Sudbury		
Question 29:	Baseline = 5.0	6 months = 4.9
Question 30:	Baseline = 4.9	6 months = 4.8

Quality of Life Data

Vancouver

 3/23 reported visual changes (one with cataracts)
 4/23 reported decreases in hearing acuity (one patient requiring tubes after 1st HBO dive)

Sudbury

1/30 reported decreased hearing acuity; no visual changes

Osteoradionecrosis

A Review of Pathophysiology, Prevention and Pharmacologic Management Using Pentoxifylline, Alpha-Tocopherol and Clodronate (Pentoclo) Rivero, Shamji and Kolokythas, OOOO Volume 124, No. 5, November 2017

- Review of proposed mechanisms of ORN, various staging classification systems, traditional vs medical management
- Conclusions that there is a lack of scientific evidence to explain the pathogenesis of ORN; therefore, a lack of efficacious conservative management strategies
- Preliminary studies using Pentoclo have been promising but additional research needed to elucidate role of pharmacologic therapy in the management of ORN

Pentoclo – Early Publications

Delanian et al; Journal of Neurological Sciences 275 (2008): 164-66





Journal of the Neurological Sciences



Significant clinical improvement in radiation-induced lumboiaceal polyradiculogathy by a treatment combining pentusifylline, tocopherol, and clodronate (Pentoclo)

Sphie Dekenar **, Joon-Jusin Lekin *, Theory Manumole *, Francois Salachur *, Pierre-Bangeis Pradar * Sounda caracterizati region caracterizati fonte.
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Delanian et al; Int Journal Rad Onc Biol Phys 80(3), 832-39, 2011



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Patient CF









CBCT Results

May 2016

November 2016



Issues – Patient CF

- Worsening bone loss despite conservative management and HB0 (70 dives total)
 - Surgeon reluctant to extract 48/47 for fear of jaw fracture; worsening or reinitiating ORN
 - Patient essentially asymptomatic since starting Pentoclo protocol despite no objective improvements; doesn't want to be on meds indefinitely
 - Should we extract tooth/teeth? Bone biopsy or other diagnostic tests?

Patient TS

August 2016 Pre-HBO

March 2017 Post-30 dives HBO



TS – Cone Beam CT

March 29, 2017



March 29, 2017



Issues – Patient TS

- Patient lives and works in Brunei with limited access to specialized care (Singapore for oncologic care)
- Very minor improvement (??)since completing 30 dives of HBO; pathologic fracture evident on March 2017 CBCT
- Patient remains asymptomatic despite radiographic change
 - Patient now on Pentoclo. Other management strategies?

Pentoclo Protocol

Medication* Prednisone Amoxicillin/ Clavulinic Acid Ciprofloxacin Fluconazole Dose 20 mg 2 g/ 500 mg 1g 50 mg Frequency Daily Daily Daily Daily

Medication* Pentoxifylline Vitamin E Vitamin E Clodronate Ciprofloxacin Prednisone

PENTOCLO

DoseFrequency400 mgTwice daily, five days per week600 IUEach morning, five days per week400 IUEach evening, five days per week1600 mgDaily, five days per week1 gOn remaining two days per week20 mgOn remaining two days per week

IU- International Units All medications taken orally.

Conclusions

- Using classic definition, ORN appears to occur at a similar rate (< 5%) regardless of whether prophylactic HBO is used or not
 - QofL scores higher at 6 months in HBO-treated group
- Visual changes more commonly reported in patients treated with HBO
- Doing prospective clinical trials in oncology is challenging!!

Thoughts

- Medical management to prevent peri-extraction and to treat post-extraction ORN should be considered as an alternative to HBO
 - Bone biopsies should be considered at time of extraction in post-XRT setting

 Definition of ORN should be expanded to include radiographic changes w/o frank bone exposure (ASCO Guideline Development)

Questions?

Vancouver

Sudbury



