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 Cancer (Vancouver)
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

<table>
<thead>
<tr>
<th>Modality</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional RT</td>
<td>7.4%</td>
</tr>
<tr>
<td>Intensity Modulated RT</td>
<td>5.2%</td>
</tr>
<tr>
<td>Chemo-radiotherapy</td>
<td>6.8%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

Adapted from Peterson, Hovan et al, 2010

4) Peterson, Hovan et al, Support Care Cancer, 2010
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

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
% TcPO

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 1 yr 2 yrs 3 yrs

Hyperbaric oxygen session No - time

- TcPO2 (LSICS) n = 34
- TcPO2 (MPRF) n = 34

% initial (LSICS)
(p < 0.01)
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)

- HBO increase blood-tissue oxygen gradient
- Fibroblast proliferation, angiogenesis, collagen formation
  - Bactericidal & bacteriostatic

### Vancouver HBU Statistics

#### # Treated 2016-2017 (23 months)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Radiation Injury</td>
<td>69</td>
</tr>
<tr>
<td>Problem Wounds</td>
<td>47</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>36</td>
</tr>
<tr>
<td>Decompression Sickness</td>
<td>25</td>
</tr>
<tr>
<td>Chronic Refractory Osteomyelitis</td>
<td>13</td>
</tr>
<tr>
<td>Sensori-Neural Hearing Loss</td>
<td>9</td>
</tr>
<tr>
<td>Gas Embolus</td>
<td>9</td>
</tr>
<tr>
<td>Necrotizing Soft Tissue Infections</td>
<td>7</td>
</tr>
<tr>
<td>Clostridial Myonecrosis</td>
<td>5</td>
</tr>
<tr>
<td>Compromised Flaps / Grafts</td>
<td>2</td>
</tr>
<tr>
<td>Severe Blood Loss Anemia</td>
<td>1</td>
</tr>
</tbody>
</table>
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

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

PAUL M. LAMBERT, DDS,* NANCY INTIERRE, DMD,† AND RALPH EICHTSTAEDT, DDS

Dental management of patients who are about to receive, or who have completed a course of therapeutic radiation involving the jaws, remains a perplexing problem. The center of debate is whether to extract teeth 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 complications associated with head and neck radiation, osteoradionecrosis (ORN).

Tumorigenic levels of irradiation damage all tissues exposed. The accepted cause of ORN is progressive obliterator endarteritis 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%. The causal relationship between dental extractions and ORN has been discussed by several authors. Reumer et al reported that the most common factors associated with ORN were postirradiation extractions (26.5%), spontaneous bone exposure associated directly with the dentition secondary to dental disease (22.8%), and preradialization extractions (20.4%).

In an effort to prevent ORN, Marx et al proposed prophylaxis with hyperbaric oxygen (HBO) before postirradiation dental extractions. In a multicenter trial, 74 patients were randomized to receive one of two treatments. One group received penicillin prophylactically 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 elevators and forceps delivery with minimal alveoplasty 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. There were 37 socket wounds in 37 patients in the antibiotic group and 156 socket wounds in 37 patients in the HBO group. In the antibiotic group, 31 sockets (22.6%) in 11 patients (22.9%) were positive for ORN, while 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. Maxey et al performed 449 extractions in 72 irradiated (25 to 84 Gy) patients. All extractions were performed without HBO, and no ORN developed during the follow-up period (median, 4.8 years).

In view of these findings, an important question remains with an unclear answer. Should unretrievable teeth be extracted before radiation therapy, after therapy with HBO prophylaxis, or after radiation therapy without HBO prophylaxis? This article presents data from our own experience with prophylactic HBO for dental extractions and reviews the pathophysiology of ORN.

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

LEWIS CLAYMAN, DMD, MD*"
Controversy: HBO for post-RT extractions?

**For**

- Marx trial (1985)
  - 74 patients for exo
    - 37 abx + HBO
  - This remains the only randomized trial to-date to study this effect

<table>
<thead>
<tr>
<th>Protocol</th>
<th>ORN Incidence</th>
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</thead>
<tbody>
<tr>
<td>Abx + HBO</td>
<td>5.4%</td>
</tr>
<tr>
<td>Abx</td>
<td>29.9%</td>
</tr>
</tbody>
</table>

**Against**

Systematic reviews:
   - 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 guideline possible.”

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(1) Peterson, Hovan et al, Support Care Cancer, 2010
### Controversy: HBO for post-RT extractions?

#### For

- Marx trial (1985)
  - 74 patients for exo
    - 37 abx + HBO
    - 37 abx (no HBO)

#### Against

Systematic reviews:

(19 studies)

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<tr>
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</thead>
<tbody>
<tr>
<td>Abx + HBO</td>
<td>4%</td>
</tr>
<tr>
<td>Abx</td>
<td>6%</td>
</tr>
</tbody>
</table>

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

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

Controversy: HBO for post-RT extractions?

**For**

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

**Against**

Systematic reviews:
3. Chuang, 2011. (14 studies)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>ORN Incidence</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abx</td>
<td>0-29.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Abx + HBO</td>
<td>0-11%</td>
<td>4.1%</td>
</tr>
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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
Study Design

• 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

• 23 patients enrolled; 22 evaluable for QofL
• 17 male; 6 female
• Age range 45-80 (62.2)

Sudbury

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

**Sudbury**

- 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


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
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

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>20 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Amoxicillin/Clavulinic Acid</td>
<td>2 g/ 500 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1g</td>
<td>Daily</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>50 mg</td>
<td>Daily</td>
</tr>
</tbody>
</table>

**PENTOCLO**

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>400 mg</td>
<td>Twice daily, five days per week</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>600 IU</td>
<td>Each morning, five days per week</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
<td>Each evening, five days per week</td>
</tr>
<tr>
<td>Clodronate</td>
<td>1600 mg</td>
<td>Daily, five days per week</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 g</td>
<td>On remaining two days per week</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20 mg</td>
<td>On remaining two days per week</td>
</tr>
</tbody>
</table>

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

• QoL 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