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**Effects of Hyperbaric Oxygen on Tissue Altered by Radiation**

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**GOALS & OBJECTIVES**

**Goal:**

The purpose of this activity is to enable the learner to identify the benefits in using hyperbaric oxygen (HBO) on tissue altered by radiation.

**Objectives:**

- Define hypoxia and describe the role of HBO in reversing hypoxia
- List effects of radiation on the skin and bone
- Discuss the how hyperbaric oxygen assists radiated tissue to heal.
- Identify the various clinical presentations of both osteoradionecrosis and soft tissue radionecrosis.
- Value the financial efficacy of hyperbaric oxygen versus conventional therapies

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**Hyperbaric Oxygen Therapy**

HBO Therapy uses 100% oxygen breathed at increased atmospheric pressure.

- A patient is enclosed in a chamber
- Atmospheric pressure is increased
- Typically pressure is 2.0 – 2.5 Atmospheres Absolute (ATA)
- 100% oxygen is breathed
- Typical treatment length is 2 hours

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**Approved uses of HBO (UHMS Hyperbaric Oxygen Therapy Indications)**

- Air or Gas Embolism
- Carbon Monoxide
- Gas Gangrene
- Crush Injury
- Acute Traumatic Ischemias
- Decompression Sickness
- Exceptional Blood Loss Anemia
- Necrotizing Soft Tissue Infections
- Chronic Refractory Osteomyelitis
- Delayed Radiation Injury
- Compromised Skin Grafts and Flaps
- Central Retinal Artery Occlusion
- Enhancement of Healing in Selected Problem Wounds

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Chamber Description

- Single patient or monoplace
- Two patient or dualplace
- Multiple patients or multiplace

Possible Side Effects

HBOT has few side effects but may include:
- Barotrauma
  - ears, sinus, teeth, chest, GI
- Temporary vision changes
- Fatigue
- Seizures (CNS O2 toxicity)
- Claustrophobia
- Paresthesia

Four Mechanisms of HBO

1. Mechanical Effects — Affects size of gas molecules
2. Hypoxia — Supply oxygen to tissues that are lacking/cellular effects of oxygen
3. Bactericidal/Bacteriostatic Effects — Oxygen as an antibiotic
4. Poisoning — Reverse effects of carbon monoxide and cyanide

Addressing Hypoxia

- Oxygen as a metabolite
  - Increases angiogenesis
- Oxygen as a cell signal
  - Stimulates macrophages to release VEGF
  - Growth factor availability

Increased growth factor availability and new blood vessel formation aid tissue repair

Mechanism #2 - Hypoxia

Addressing Hypoxia

- Oxygen as a metabolite
- Oxygen as a cell signal

Assessing Hypoxia

Lower Extremity Assessment
- Temperature of skin
- Pulses
- Presence of hair
- General tissue appearance
- Skin Perfusion Pressure
- Transcutaneous Oxygen Measurement
Transcutaneous Oximetry

Transcutaneous Oxygen Measurement (TCPO2)

- Non-invasive vascular test
- Electrodes placed on skin in the areas to be assessed
- Measures the partial pressure of oxygen in the tissue in mmHg

Measuring Tissue Oxygen

What can it tell us?

- If wound healing is compromised by hypoxia
- If the hypoxia is reversible
- If the patient is likely to respond to the HBOT
- If the patient has reached a therapeutic level
- Which amputation site is most likely to heal post-operatively

Hypoxia and HBO

Approved Hypoxic Conditions:

- Acute Peripheral Arterial Insufficiency
- Acute Traumatic Peripheral Ischemia
- Compromised Flaps and Grafts
- Crush Injuries
- Delayed Radiation Injury
- Central Retinal Artery Occlusion
- Enhancement of Healing in Selected Problem Wounds

HBO and Radiation...They Have History

- Monoplace chambers were developed to treat tumors with radiation and HBO in the late 1950’s early 60’s
- Tumors were noted to be much more susceptible to radiation in a hyperbaric environment
- Not practical; radiation is brutal on the acrylic, patient positioning, etc...
- Better radiation delivery methods were developed

Radiation Dosing

Rads & Grays

1 rad = 1 centi Gray (cGy)

= 100 ergs of energy / gm of tissue

The biological effect is

- DNA Damage
- Lipid peroxidation
- Protein denaturation

The cellular consequences

- Death
- Dysfunction

1.2 million new cases of invasive cancer will be diagnosed this year in the United States.

Half of these patients will receive radiation therapy as part of their management.

Serious radiation complications will occur in up to 5% of patients receiving radiation.

This could represent

30,000 cases / year
Cell Sensitivities (Descending order)

- Tumor
- Endothelium
- Fibroblasts
- Muscle
- Nerve

Radiation Effects

Acute Effects
- Erythema
- Pigmentation changes
- Hair loss
- Skin erosions

Supportive Care (Self limited)
- Antibiotics if cellulitis

Bone is 1.8 x density of soft tissues (greater energy absorption)
- Mandible very susceptible - greater bone density & lower vascularity

Isodosing Concept
- Tumor - conceptually treated as a spheroidal mass with the greatest number of target cells at the center
- A boost dose is given to the center
- At incremental distances from the tumor’s center, the mass is less & therefore the delivered dose is less
- Additional "diffusion" of injury from beam divergence

"A shallow oxygen gradient forever commits irradiated tissue to exist at a lower tissue perfusion level"

Robert Marx - 1982
**Rabbit Ear Chamber**

Normal Conditions
Membrane closed
Central Hypoxia

“Central” Hypoxia
Membrane Open
No oxygen gradient
Becomes a “problem wound”

Loss of the oxygen gradient arrests healing

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**Radiation Wounds**

- A progressive, proliferative, endarteritis
- Obliterative process
- Destroys tissue blood supply
- Hypoxic, fibrotic legacy

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**Radiation Tissue Injury vs Time**

TCPO₂, Normal (ICS) / Radiation Portal Granstrom G 1993 XIXth Annual EUBS Meeting

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**Blood flow in Non-Irradiated bone**

Granstrom G 1993 XIXth Annual EUBS Meeting

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**Blood flow in Irradiated bone**

Granstrom G 1993 XIXth Annual EUBS Meeting
There is no satisfactory treatment of radiation necrosis using conventional therapies. It is difficult to provide adequate nutrients & oxygen to devascularized tissues & surgical reconstruction has a high failure rate due to healing problems.

How does HBO help radiation damaged tissue?

1.0 ATA Air

\[ \Delta = 10-20 \text{ mmHg} \]

Kindwall and Whelan (2008)

HBO - 2.5 ATA

\[ \Delta = 230 \text{ mmHg} \]

Kindwall and Whelan (2008)

Plateau Phase

Granstrom G 1993 XIXth Annual EUBS Meeting

Vascular Density % of normal

Granstrom G 1993 XIXth Annual EUBS Meeting
Blood flow in Irradiated bone
Granstrom G 1993 XIXth Annual EUBS Meeting

Blood flow in Irradiated bone after HBO & bone grafting
Granstrom G 1993 XIXth Annual EUBS Meeting

What are the common clinical indications?

Osteoradionecrosis of the Mandible (ORN)
Prevention & Treatment
Soft Tissue Radionecrosis

Radiation Injury Complications
- Intractable pain
- Drug dependency
- Trismus (jaw contractures)
- Nutritional deficiencies
- Pathologic fractures
- Oral and cutaneous fistulas
- Loss of large areas of soft tissue and bone

Radiation Injury Complications
- Need for frequent blood transfusions
- Hematuria with urgency
- Bloody diarrhea
- Loss of bladder control
- Odor
- Body image issues
- Quality of life adversely affected
- Traditional treatment is palliative at best
**ENT Radiation Injuries**

- Xerostomia (dry mouth)
- Aphagia/aspiration
- Candidiasis
- Radiation caries
- Hypoplasia of developing teeth (children)
- Worse with time never better
- Rapid mitosis in the periosteum leads to the vasculitis

**Radiation-Induced Hemorrhagic Cystitis**

- 40 patients with biopsy-proven radiation cystitis and severe hematuria.
- Hematuria disappeared completely or improved in 37 patients after treatment
- Recurrence rate was 0.12 patients/year

Beavers RFM, Bakker DJ, Lancet 1995; 346: 803-05

**Radiation Proctitis Treated with HBO**

- HBO responders
- Non-responders

Warren DC, Undersea Hypert Med 1997 Sep;24(3):181-184

**HBO for Severe Laryngeal Necrosis: A Report of Nine Consecutive Cases**

- Eight of nine patients had a Chandler grade IV necrosis and the ninth had grade III necrosis
- All patients maintained their voice until death
- All patients with tracheostomies were decannulated
- All patients with fistulae had successful closure


**Cerebral Radionecrosis Managed w/ HBO**

- Two pts w/ AVMs treated with Gamma Knife radiosurgery & had developed imaging signs consistent with radionecrosis. They were treated at 2.5 ATA x 60 min – 40 sessions.
- Both responded well to HBO, one lesion disappeared & the other was reduced significantly in size.
- No adjuvant steroids were given.

HBO & radiation-induced brain injury in children

Patients presented with new or increasing neurologic deficits associated with imaging changes after radiotherapy. Necrosis was proven by biopsy in eight cases.

Histologic types:  
- brain stem glioma (n = 2)  
- ependymoma (n = 2)  
- germinoma (n = 2)  
- low grade astrocytoma (n = 1)  
- oligodendroglioma (n = 1)  
- glioblastoma multiforme (n = 1)  
- arteriovenous malformation (n = 1)

Sites of radiation necrosis:  
- brain stem (n = 2)  
- posterior fossa (n = 1)  
- supratentorial fossa (n = 7)


RESULTS:

Initial improvement or stabilization of symptoms and/or imaging findings were documented in all ten patients studied.

Diagnosing Osteoradionecrosis

Exposed bone in previously irradiated tissue that has failed to heal spontaneously, or with treatment, for at least six months.

- Johnson 1992

Non-healing wound of more than 1 cm within an irradiated field, involving mucosa or skin, & with denuded bone, that has persisted for more than 3 months despite conservative tx

- Granstrom 1992

Osteoradionecrosis vs Radiation Dose

Retrospective review of 104 cases

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5,000 cGy</td>
<td>5</td>
</tr>
<tr>
<td>5-6,000 cGy</td>
<td>24</td>
</tr>
<tr>
<td>6-7,000 cGy</td>
<td>33</td>
</tr>
<tr>
<td>&gt; 7,000 cGy</td>
<td>42</td>
</tr>
</tbody>
</table>

89.4% trauma-induced  
10.6% spontaneous

Osteoradionecrosis vs Time

Clinical Damage  
- Acute  
- Surgical Trauma  
- Mechanical Trauma  
- Nutrition Infection

Subclinical Damage

Years  
- Recovery

Clinical Threshold

Rubin P, Casarett GW 1968

Radiation Tissue Injury vs Time

TCPO₂ Left Intercostal Space/TCPO₂ Radiation Portal

RTI - Control Group  
RTI - HBO Group

Years  
- Marx RF (Kindwald 2000)
Hyperoxia-induced Angiogenesis

<table>
<thead>
<tr>
<th>ATA Oxygen</th>
<th>Tissue Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>1.50</td>
<td>0.12</td>
</tr>
<tr>
<td>1.75</td>
<td>0.25</td>
</tr>
<tr>
<td>2.00</td>
<td>0.43</td>
</tr>
<tr>
<td>2.50</td>
<td>0.74</td>
</tr>
<tr>
<td>3.00</td>
<td>0.91</td>
</tr>
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</table>

Marx RE, HBO 1993

Prevention of Osteoradionecrosis

**Randomized Prospective Clinical Trial**

*Marx RE JADA 1985; 111:49-54*

**Purpose**

Test the hypothesis of whether or not HBO can prevent the development of ORN after tooth removal in patients with prior radiation.

Prevention of Osteoradionecrosis

**Randomized Prospective Clinical Trial**

*Marx RE JADA 1985; 111:49-54*

<table>
<thead>
<tr>
<th></th>
<th>No Pts</th>
<th>No Teeth</th>
<th>ORN Sockets</th>
<th>ORN Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN Group</td>
<td>37</td>
<td>135</td>
<td>31 (23%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>HBO Group</td>
<td>37</td>
<td>136</td>
<td>4 (3%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

*Pre-op HBO reduces the incidence of ORN from 30% to 5%. We conclude that HBO should be used prior to any extractions.*

Marx Protocol

- **Basis for 20 pre-op. procedures**
  - plateauing of angiogenesis
- **Basis for 10 post-op. procedures**
  - reduced wound dehiscence by promoting collagen production along incision lines and fixture surfaces
  - assistance in graft survival and early revascularization by intermittent reversal of inherent hypoxia in surgical wounds

The Clinical Experience

HBO & Radiation

- **Timing of preoperative HBO therapy is not critical**
  - “Delays of up to one year between HBO & surgery have not compromised results”

- *Marx 1991*
Randomized Prospective Clinical Trial of Surgical Procedures in the Irradiated Field

Marx RE 1993

- 80 control patients
- 80 HBO patients (Marx Protocol)

All high risk (>6,400 cgy)

Complications of surgery in irradiated tissue

<table>
<thead>
<tr>
<th></th>
<th>Minor</th>
<th>Major</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEHISCENCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12 (15%)</td>
<td>26 (33%)</td>
<td>38 (48%)</td>
</tr>
<tr>
<td>HBO</td>
<td>6 (7.5%)</td>
<td>3 (3.5%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6 (7.5%)</td>
<td>13 (16%)</td>
<td>19 (24%)</td>
</tr>
<tr>
<td>HBO</td>
<td>3 (3.5%)</td>
<td>2 (2.5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td><strong>DELAYED HEALING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>44 (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBO</td>
<td>9 (11%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Radiation Injury

Initial photo
After 5 hyperbaric treatments
After 13 hyperbaric treatments
After 36 hyperbaric treatments

"Osteoradionecrosis is best managed with hyperbaric oxygen alone, or in conjunction with surgery."

...in high-risk patients, pre-extraction hyperbaric oxygen should be considered

HBO Benefits Radiation Injuries

- **PRESSURE** -- 2.5 ATA Pre and Post-op with air breaks
- **DURATION** -- 90 minutes at depth
- **FREQUENCY** -- Daily

Clinical Considerations:
- For planned surgical procedures, timing is unimportant
- Air breaks required for 2.5 ATA treatment
- **Treatment Threshold:** 20 – 60 Treatments
- **Marx Protocol:** 20 treatments – procedure – 10 treatments

National Cancer Institute Monographs 1990: No 9

"Osteoradionecrosis is best managed with hyperbaric oxygen alone, or in conjunction with surgery."

Economic Efficacy
**HBOT is Cost Effective for ORN**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Average one year costs</th>
<th>Average total costs</th>
<th>Resolution rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON HBOT</td>
<td>116</td>
<td>$47,000</td>
<td>$162,000</td>
<td>10%</td>
</tr>
<tr>
<td>HBOT w/o Surgery</td>
<td>88</td>
<td>$40,000</td>
<td>$83,000</td>
<td>18%</td>
</tr>
<tr>
<td>MARX-UM protocol</td>
<td>492</td>
<td>$49,000</td>
<td>$49,000</td>
<td>100%</td>
</tr>
<tr>
<td>MARX-UM Protocol used in Private practice</td>
<td>112</td>
<td>$45,000</td>
<td>$45,000</td>
<td>100%</td>
</tr>
</tbody>
</table>

U M = University of Miami  
Johnson, ET Al, 1994. Updated April 2004 in a presentation in Boynton Beach, FL.

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**Cochrane Systematic Review - 2005**

These small trials suggest that for people with late radiation tissue injury affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcomes. HBOT also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field.


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**Common Concerns**

**Malignant tumors**
- Early concerns
- No effect on animal models for cancer
- No evidence for harm

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**Summary**

- Indication is supported by PRT data
- Deemed to be a “Standard of Care” by NCI
- The weight of current evidence, as derived by randomized trials, favors use of HBO
- Demonstrated “financial” effectiveness
- No proven alternative therapies

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**Questions?**

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**References**

References


