HYPERBARIC OXYGEN AND THE CANCER PATIENT: WHAT ARE THE POSSIBILITIES

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FACULTY DISCLOSURE INFORMATION

Dr. John J. Feldmeier is a member of the International ATMO speakers bureau and serves as a corporate consultant

MONOPLACE CHAMBERS

In monoplace chamber, single patient treated. The entire chamber is pressurized with 100% O2. Usually at 2.0 Atmospheres pressure

PRIMARY MECHANISMS FOR HBO2

1. Pressure shrinks volumes of trapped gas according to ideal gas laws (volume inversely proportional to pressure)
2. Hi ppO2 Dissolves additional oxygen in plasma (enough to sustain life without hemoglobin)
EFFECTS OF HBO₂

- Hyperoxygenation/Normalization of Tissue Oxygenation (life without blood)
- Pressure & Gas Gradients - allowing diffusion of gas from bubbles in air embolism and decompression sickness
- Vasocostriction - useful in edema (crush injury and cerebral edema)
- Altered Cellular Function
  - Enhanced WBC killing
  - Decreased WBC adhesion (prevention of ischemia/reperfusion)
  - Increased in growth factors and receptors
  - Mobilization of stem cells
- Angiogenesis

BEGINNING IN THE 1970'S THE ROBERT MARX DDS CONTRIBUTION TO THE UNDERSTANDING OF HBO₂ IN THE TREATMENT OF DELAYED RADIATION INJURY

- The introduction of the 3H tissue effects
  - Hypovascular, hypocellular and hypoxic
- 1. Recognition and definition of the pathogenesis of OEB - not an infection
- The importance of Pre-Op HBO₂
- The need to eradicate all dead bone
- Establishment of staging system that determines treatment plan
- Post-op treatment

LATE INJURIES

- The fibroatrophic effect popularized by Sylvia Dejainian de-emphasizes the vascular effects
- Marx’s 3H tissues - “hypocellular, hypoxic and hypovascular”
- Reports of radiation injury still observe vascular effects
- With aggressive combined chemorads protocols more frequent reports of “consequential” effects where acute injuries are not self-limited and acute changes transform to late injuries without a latent period

Delivery of Radiation and Release of Cytokines and Other Bioactive Agents (TGF-beta, IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-alpha, GMCSF, MMP-3, MMP-9, and TIMP-1).

Normal Tissues 
Acute Injury

If Severe Enough, Consequential Effects

Delivery of Radiation

Late Effects that lead to Chronic Pathology

Evolving Vascular and Fibroatyrophic Effects

Thom SR. Plast Reconstr Surg 2011

HYPERBARIC OXYGEN

Angiogenesis with elaboration of growth factors
Reduction of Fibrosis
Induction and Mobilization of Stem Cells

Resolved or Prevented Radiation Necrosis
American Osteopathic College of Occupational and Preventive Medicine
OMED 2016 Didactic Sessions.

Hypoxic, hypo-vascular, hypo-cellular environment
Pre-HBO2

More cells
And more blood vessels
Post-HBO2

Angiogenesis in Irradiated Tissue

ANECDOTALLY

Head and neck patients treated for mandibular ORN or soft tissue necrosis demonstrate a significant softening of tissues within radiation high dose region demonstrating woody fibrosis and even an improvement in hyperpigmentation
American Osteopathic College of Occupational and Preventive Medicine
OMED 2016 Didactic Sessions.

HYPERBARIC OXYGEN PROPHYLAXIS OF RADIATION INJURY: ANIMAL RESEARCH

• Feldmeier et al (Radiother Oncol 1995;35:138-144) demonstrated success in applying HBO to reduce radiation enteropathy in murine model of small bowel.

DIFFERENCE IN COATS WITHOUT/WITH HBO

Increased Cellular Survival, in this case Melanocytes

FINDING / NUMBER OF ANIMALS

<table>
<thead>
<tr>
<th>Finding</th>
<th>Rads only</th>
<th>Rads+HBO</th>
<th>No rads</th>
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<tbody>
<tr>
<td>White</td>
<td>8</td>
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</tr>
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<tr>
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<td>3</td>
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<tr>
<td>Total</td>
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<td>3</td>
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RESULTS BY EVERY ASSAY SHOWED PROTECTIVE EFFECT

• Stretch assay showed better compliance
• Histologic staining showed more collagen in the bowel wall of animals not receiving HBO
• Morphometry showed gross changes in radiation only animals and almost none in HBO animals

INTRIGUING WORK FROM STEVE THOM’S GROUP THEN AT PENN

• It has been shown that stem cells can be induced and mobilized by HBO2 through induction of nitric oxide initially in a model of diabetes and now including a model of radiation injury
STEM CELL MOBILIZATION BY HYPERBARIC OXYGEN

CLINICAL PUBLISHED HBO2 EXPERIENCE IN THE FOLLOWING ENTITIES

- Osteoradionecrosis of the Mandible
- Soft Tissue Necrosis of the Head and Neck
- Radiation Cystitis
- Radiation Proctitis/Enteritis
- Radiation Induced Brain Necrosis
- Radiation Induced Xerostomia
- Chest wall necrosis
- Extremity Necrosis
- Soft Tissue and Bony Necrosis of the Abdomen and Pelvic
- Neurologic Injury-plexopathy

SYSTEMATIC REVIEW

- 74 papers
- 67 positive reports
- of the 7 negative reports 4 nervous system including CNS (1 each in mandible ORN, cystitis and extremity)
- Nervous System included
  - RCT Pritchard Brachial Plexopathy (Radiother Oncol 2001)
  - Optic Neuritis Roden (Optimalmology 1990)
  - Radiation Myelitis Hart (Cancer 1976-actually mixed with no motor improvement)
- Hind brain necrosis Cirafci( Int J Neuro Sci: 1999 single case no improvement)
Woody Fibrosis
Post rads in H&N CA patient

Exposed Cartilage
Initiation of TX

Midtreatment

End of TX
Post Flap and Graft

NEOVIUS H&N STUDY
KAROLINSKA INSTITUTE

• 15 patients in each group
• HBO Group:
  □ Matched pair historic controls
  □ Healing in 12/15; 2 improved; 1 non-healing
• Non-HBO Group:
  □ Only 7/15 Healed; 1 fatal bleed

MARX SOFT TISSUE H&N TRIAL

• 160 patients: 50% with; 50% without HBO
• In terms of following outcome parameters outcome is highly significant statistically:
  • Wound Infection 6% vs 24%
  • Wound dehiscence 11% vs 48%
  • Delayed Healing 11 vs 55%

CNS-BRAIN NECROSIS

• Koshi K 2003 Case report of brain necrosis
• Patient had had 2 crises of Stereotactic Radiosurgery to the same lesion in the left cerebellum
• He developed dizziness and ataxia
• MRI showed a cystic area with peripheral enhancement
• Had 2 crises of HBO for a total of 110 txs at 2.5 ATA for 60 minutes (he had had temporary improvement after the 1st crse)
• After 2nd crse MRI and neurologic sx stabilized

W-6
**CNS-BRAIN NECROSIS-2**

- Case report UHMS 2009 Abstract Only
- Pons et al report 63 y/o patient with biopsy proven brain necrosis in suprasellar region after resection of cranipharyngioma followed by ext beam rads additionally had radioactive P-32 injected into cyst after tumor recurrence
- Received 40 HBO2 txs at 2.0 ATA for 120 minutes
- Clinically gradual improvement with resolution of cognitive and personality changes
- MRI also improved

**CNS-INJURY RADIATION MYELITIS**

**Material and Method:** A 51-year-old female patient with a diagnosis of multiple myeloma in 2006 received a dose of 30 Gy to a spinal field encompassing vertebral levels T6-L1. The patient had had thalidomide and Decadron prior to radiation as systemic therapy. She underwent two stem cell transplants at the University of Michigan by December 2007, and some two years later developed the onset of back pain and tingling in the left lower extremity, and motor/sensory loss in the right lower extremity (an incomplete Brown Séquard’s syndrome). Spinal MRI demonstrated a non-specific signal increase on T-2 weighted images at vertebral level T-8 and T-12 felt to be consistent with but not pathognomonic for radiation induced myelitis. The patient was evaluated (e.g. CXR) and began daily Hyperbaric Oxygen Therapy (HBOT) consisting of 2.5 ATA, 90 minutes, with air breaks.

**OUTCOME MYELITIS TX**

By twelve HBOT visits she had adverse effects on her vision; with improved motor function in the right lower extremity. By twenty four HBOT visits her lower extremity(s) subjective and objective findings had stabilized and she was able to travel to a family reunion. Upon restart of HBOT (treatment #35) her vision had returned to normal, and she was capable of participating in physical therapy with improved motor function in her right lower extremity. By 40 HBOT visits her right foot drop had resolved. She was discharged from the HBO department.

- Serial MRIs show resolution

**Radiation Cystitis**
RADIATION CYSTITIS

• This can be a life threatening disorder
• Usual initial treatment for hemorrhagic cystitis is chemical or electro cautery
• Adds another noxious insult to already injured tissues
• Sometimes requires cystectomy and ileal loop

CYSTITIS UPDATE

• 19 papers in the review
• Only 1 negative trial
• 2 additional case reports
• The Virginia Mason Group now with the largest series-60 pts.
  • 18 resolved; 26 partial response; 8 unchanged; 2 progressive

MINI META-ANALYSIS

• All publications of 257 reported
• 186 or 76.3% improved

EUROPEAN CONSENSUS CONFERENCE IN LISBON OCTOBER 2001

Considered Radiation Cystitis Second only to Mandibular ORN in terms of strength of evidence
### HBO\(_2\) FOR RADIATION CYSTITIS

- 57 patients treated for hemorrhagic radiation cystitis
- 49 (86%) experienced complete resolution or marked improvement in hematuria
- When performed, 77% had objective improvement on post-HBO\(_2\) cystoscopy
- When treated < 6 months after onset of hematuria, 96% response

Corman JM. J Urol 2003
Chong KT. J Urol 2005

### PROCTITIS AND ENTERITIS

- Combined often for the purpose of reporting
- The small bowel has inherently lower tolerance to radiation compared to large bowel
- Clinical incidence of proctitis is higher due to relative increased frequency of radiating pelvic tumors (GYN, prostate, rectum)

### ENTERITIS AND PROCTITIS

**FELDMEIER-HAMPSON REVIEW**

- 14 papers found
- 12 are case series (AHA 5; NCI 3)
- 2 animal studies by Feldmeier et al

### RADIATION ENTERITIS

- Bredfeldt and Hampson (Am J Gastroentero 1998;93:9) report 19 patients with chronic radiation enteritis: 47% resolution; 37% improvement and 16% no improvement
- Animal study by Feldmeier et al (Radiother Oncol 1998;35:138-144) successful prevention of enteritis

### HYPERBARIC OXYGEN TREATMENT OF CHRONIC REFRACTORY RADIATION PROCTITIS: A RANDOMIZED AND CONTROLLED DOUBLE-BLIND CROSSOVER TRIAL WITH LONG-TERM FOLLOW-UP

- 150 patients randomized to 30-40 HBO\(_2\) treatments at 2.0 ATA vs. air at 1.1 ATA
- Sham patients then crossed over to HBO\(_2\)
- 120 completed study protocol
- Healed or improved:
  - 89% HBO\(_2\) group vs. 62% in sham group (p=0.0009)
  - Absolute risk reduction 33%, resulting in NNT=3
  - Marked improvement in bowel-specific QOL in HBO\(_2\) vs. sham group

Clarke RE. Int J Radiat Oncol Biol Phys 2008

### Radiation Proctitis

Leiper K. Clin Oncol 2007
American Osteopathic College of Occupational and Preventive Medicine
OMED 2016 Didactic Sessions.

Oliai C. Int J Radiat Oncol Biol Phys 2012

Glover M. Lancet Oncol 2015

Hampson NB, Holm JR. Cancer 2012

ISSUES OF TREATMENT

- Dose:
  - Pressure: Marx has shown dose response in animal model for increasing pressure
  - Number of treatments: Often 40 or more are required
  - Peer review is recommended after 60 treatments
  - Publication by Hampson et al from VMMC showed successful treatment generally requires 40 sessions
  - Peer review is recommended after 60 treatments
  - Carcinogenesis: No convincing evidence in either animal studies or clinical reports
  - Experience with radiation sensitization
  - Animal studies
  - Experience treating patients with radiation injury
Hyperbaric Oxygen: Does it promote growth or recurrence of malignancy?

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Feldmeier JJ, Undersea Hyperb Med 2004

ARE HBO BENEFITS SUSTAINED?

• In our continuous fight to maintain the HBO2 indication of radiation injury (necrosis) long term follow-up is needed

• Consider the following case

15 Year Follow-up
RECENT PUBLISHED RESULTS OF HYPERBARIC OXYGEN IN ORN

- Marx’s most recent report in Kindwall textbook 184/184 resolved including USAF and private practice
- Non-Marx experience in 2002 article by Feldmeier and Hampson in 8 reports where resolution reported as end pt: 148 of 196 resolved (75.5%)
- The use of Marx protocol in community and Non-US environments remarkably similar results

CONCLUSIONS

- Results in Soft Radiation Necrosis are consistently positive
- If bone involved pre-op HBO and surgical removal of necrotic bone
- HBO should be combined with best surgical techniques and HBO pre-op improves the tissue milieu
- Various protocols used 2.0 VS 2.4 ATA
- In my experience and review, 40 treatments should be utilized
- Animal studies by Marx suggest an advantage for 2.4 ATA though many + results have been obtained at 2.0 ATA

A NEW APPLICATION?
PREVENTION/REDUCTION OF ACUTE RADIATION TOXICITY

- Teguh et al from Rotterdam 2009 Int J Radiat Oncol Biol
- RCT 19 pts randomized to receive HBO2 or not shortly after RT
- HBO2 was 30 txs at 2.5 ATA for 90 minutes
- QOL scores improved in significant fashion for HBO2 pts including: swallowing, dry mouth, sticky saliva, eating in public and oral pain