HOPON / DAHANCA21 – Lessons in methodology and avoiding pitfalls

(Hyperbaric Oxygen for the Prevention of Osteoradionecrosis)

European Clinical Trials Database, ID: EudraCT2007-006225-27

A randomised controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible.

Chief Investigator
Professor Richard Shaw

Liverpool Cancer Trials Unit
University of Liverpool, UK
Osteoradionecrosis

Definition:

“Irradiated bone undergoes necrosis and becomes exposed through overlying soft tissues >3 months”

Considerable morbidity, mortality & cost
Background

- Hyperbaric Oxygen (HBO) widely used in prevention

- Supporting evidence weak:
  - Marx et al. randomized trial, significantly improved rate of osteoradionecrosis for HBO in irradiated tooth sockets following dental extraction (RR 1.4; 95% CI 1.1 to 1.7, P value = 0.009, NNT= 4)
  - Cochrane Review: HBO associated with improved outcomes
Marx 1985

- 72 patients
- Single centre
- Trial methodologies?
  - Primary endpoints
  - Randomisation
  - Inclusion
- ORN
  - 5.4% vs 29.9%
  - NNT = 4
- Control group:
  Highest incidence ORN ever seen.

Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin

Robert E. Marx, DDS
Robert P. Johnson, DDS
Stuart N. Kline, DDS

The pathogenesis of osteoradionecrosis has recently been shown to be a radiation-induced, nonhealing, and hypoxic wound rather than an osteomyelitis of irradiated bone. Since this discovery, a scientific basis for the use of hyperbaric oxygen in the treatment phase of osteoradionecrosis has been established. The data supporting the use of hyperbaric oxygen in treatment are compelling and include a proved tissue angiogenesis, collagen synthesis and thus wound healing enhancement, and several controlled but retrospective clinical studies. However, these studies have been concerned only with the treatment phase of osteoradionecrosis. To date, no studies related to the jaws have addressed a trial of hyperbaric oxygen in a prospective randomized fashion and none has addressed the prevention phase of osteoradionecrosis.

The purpose of this study was to test the hypothesis of whether the hyperbaric oxygen protocol currently established for soft tissue revascularization can prevent the development of osteoradionecrosis after tooth removal in a high-risk patient population.

Methods and materials
Three centers were chosen to participate in this study. These included a university training center, a private practice, and a military oral and maxillofacial surgery care facility as well as both multiplex and monocanal hyperbaric oxygen delivery systems. Seventy-four patients who met the following criteria were entered into the study: Patients were included who:
- Had an indication for removal of one or more teeth in a segment of the mandible that had received a documented absorbed irradiation dose of 6,000 rads or greater.
- Agreed to maintain follow-up visits for a minimum of 6 months.
- Patients were excluded who:

Control group: Highest incidence ORN ever seen.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Tooth removals in bone-irradiated to dose = 6,000 rads.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. patients</td>
</tr>
<tr>
<td>PGN group</td>
<td>37</td>
</tr>
<tr>
<td>HBO group</td>
<td>37</td>
</tr>
</tbody>
</table>

*PGN—penicillin.
HBO—hyperbaric oxygen.
Aim

• Establish the benefit of HBO in prevention of ORN following high-risk surgical procedures to the irradiated mandible

• Effect of HBO on:
  – acute symptoms after surgery
  – long-term pain
  – quality of life

• Determine the overall risk of ORN after high-risk surgical procedures
Design

• Randomised controlled phase III trial
• Patients and site investigators were unblinded, but the primary endpoint was remotely assessed by a blinded expert panel of investigators
• Conducted in 16 acute UK hospitals, one acute hospital in Denmark, and nine UK hyperbaric medicine facilities registered with the British Hyperbaric Association.
Design

High risk patients:
Require surgery to mandible with >50Gy radiotherapy

4 week run in: Eligibility, patient information, consent

Baseline assessment:
QOL, pain, photograph, radiograph

1:1 Randomisation

Allocation

Standard Management Arm:
Chlorhexidine mouthwash
Antibiotics
Surgery

Acute Symptoms Questionnaire x 7 days

Experimental Treatment Arm:
20 daily HBO dives

Chlorhexidine mouthwash
Antibiotics
Surgery

Acute Symptoms Questionnaire x 7 days

10 daily HBO dives

Follow-up

3 month follow up
Healing, QOL, pain, photograph*, radiograph

6 month follow up
Healing, QOL, pain, photograph, radiograph

12 month follow up
Healing, QOL, pain, photograph*, radiograph

Late follow up (at closure of trial)
Implant loss

Analysis

* Radiograph at 3/12 and 12/12 only if ORN present
Outcomes

- **Primary outcome (blinded)**
  - Osteoradionecrosis 6 months after surgery, determined by blinded central review of:
    - Clinical photographs
    - Radiographs

- **Secondary (blinded)**
  - Classification of ORN: modified Notani Score at 3, 6, 12 months
  - Overall incidence of ORN at 3, 6, 12 months

- **Secondary (unblinded)**
  - Acute symptoms x 8 days following surgery (pain, swelling, trismus, diet)
  - Pain, at 3, 6, 12 months
  - QOL, at 3, 6, 12 months
Results

- 144 patients randomized
- 2008-2016
- 72 HBO arm: 72 non-HBO arm
- 100 evaluable patients for primary analysis
# Primary Outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence ORN 6 months blinded</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6/100</td>
<td>6%</td>
</tr>
<tr>
<td>HBO Arm</td>
<td>3/43</td>
<td>7%</td>
</tr>
<tr>
<td>Non-HBO Arm</td>
<td>3/57</td>
<td>5%</td>
</tr>
</tbody>
</table>

OR for ORN 1.13, P >0.99*

The IDMC recommended closing after 100 evaluable patients as the rate of ORN seen was much less than that assumed, precluding statistically significant efficacy analyses for HBO.

*Two-sided Fishers Exact P>0.99 (95% C.I.:0.06 to 6.66)
Secondary Outcome (Unblinded)

- Acute Symptoms
- HBO patients reported less severe symptoms in first 7 days after surgery*
  - Pain (P=0.0458)
  - Swelling (P=0.0182)
  - Bleeding (P=0.0375)
  - Trismus (P=0.004)
  - Eating (P=0.004)
- Higher proportion (65%) of HBO arm comfortable at day 8 post-surgery than non-HBO arm (35%), OR 2.79, P=0.038#

*area under the curve analysis
*Two-sided Fishers Exact P=0.038 (95% C.I.:1.01  50  8.05)
Secondary Outcome (Unblinded)

- Late Pain
- ... at 3, 6, 12 months
- Marginally less pain in HBO arm, smallest value $P=0.046$
Secondary Outcome (Unblinded)

• Quality of Life
UW QoL Social Domain, by trial arm.
Conclusion

- Incidence of ORN after surgery in irradiated patient was only 6%
- Risk to irradiated patients is too low to justify the costs of HBO
- Incidence precludes further prevention trials in this setting
- Related to:
  - More stringent dental protocols
  - IMRT
  - Other forms conformal RT
Conclusion

• Findings reverse the conclusions of
  – Marx et al 1986
  – Cochrane review

• Financial costs and logistic demands of HBO therapy in prevention of ORN are not justified by rate of ORN

• Change in practice for those health systems where HBO is currently the standard of care
Acknowledgements:
Trial Management Group
Site Pis x 17 sites
9 HBO Facilities

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Greenlight date*</th>
<th>FirstRand date</th>
<th>LastRand date</th>
<th>HBO</th>
<th>Standard</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Hospital Aintree</td>
<td>16/9/2008</td>
<td>24/3/2008</td>
<td>16/11/2016</td>
<td>86</td>
<td>36</td>
<td>122</td>
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<tr>
<td>Liverpool University Dental Hospital</td>
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<td>18/12/2009</td>
<td>18/12/2009</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>University Hospital Birmingham</td>
<td>5/2/2009</td>
<td>27/5/2009</td>
<td>13/1/2013</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Manchester Royal Infirmary</td>
<td>16/1/2009</td>
<td>11/9/2009</td>
<td>12/2/2010</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Glen Owyd Hospital</td>
<td>21/8/2009</td>
<td>25/8/2009</td>
<td>25/8/2009</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Guys and St Thomas</td>
<td>2/3/2010</td>
<td>5/11/2012</td>
<td>5/1/2012</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>St Richards Hospital</td>
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<td>7/2/2013</td>
<td>7/2/2013</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Queen Alexandra Hospital</td>
<td>27/1/2012</td>
<td>15/3/2012</td>
<td>14/5/2014</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bristol Haematology and Oncology Centre</td>
<td>27/11/2012</td>
<td>28/1/2013</td>
<td>19/5/2013</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Copenhagen University Hospital</td>
<td>29/8/2013</td>
<td>5/9/2014</td>
<td>29/10/2015</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<tr>
<td>University Hospital of Wales</td>
<td>18/3/2014</td>
<td>2/9/2014</td>
<td>8/9/2014</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Royal Gwent Hospital</td>
<td>26/3/2014</td>
<td>16/4/2014</td>
<td>12/10/2016</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>72</td>
<td>72</td>
<td>144</td>
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</tbody>
</table>

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Clinical Investigation

HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery

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Anastios Kanatas, FRCS, † Peter Nixon, FDS, † James McCaul, FRCS, †
Prav Praveen, FRCS, ** Terry Lowe, FRCS, ††
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Tristan Cope, FRCA, ††‖ and Mark Glover, MFOM ††¶
Methodological concerns 1

- Time interval between randomisation & surgery

Delay to surgery in HBO arm:

20 dives of HBO – 4 weeks
Administrative delay – 2-3 weeks
Funding delay - variable
Methodological concerns

- Time interval between randomisation & surgery, with consequent differing rates of drop out between the two arms of the trial, and similar extension of primary endpoint.

Diagram:
- Screening
- Randomisation
- surgery
- Hyperbaric oxygen 20 dives
- HBO 10 dives
- 6 months
- Primary endpoint
- Primary endpoint

Aintree University Hospitals NHS Foundation Trust
Baseline characteristics of patients analysed per protocol

<table>
<thead>
<tr>
<th>Characteristic (Reviewed patients)</th>
<th>HBO arm (47)</th>
<th>Control arm (53)</th>
<th>TOTAL (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age yrs mean (SD)</strong></td>
<td>58.3 (10)</td>
<td>58.2 (10.4)</td>
<td>58.2 (10.1)</td>
</tr>
<tr>
<td><strong>Males, n(%)</strong></td>
<td>14 (30%)</td>
<td>14 (27%)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td><strong>Smoking, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>14 (29%)</td>
<td>17 (32%)</td>
<td>31 (31%)</td>
</tr>
<tr>
<td>Past</td>
<td>23 (48%)</td>
<td>26 (49%)</td>
<td>49 (49%)</td>
</tr>
<tr>
<td>Current</td>
<td>10 (21%)</td>
<td>10 (18%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Alcohol n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4 (12%)</td>
<td>3 (7%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Past</td>
<td>5 (15%)</td>
<td>10 (25%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Current</td>
<td>24 (72%)</td>
<td>26 (66%)</td>
<td>50 (69%)</td>
</tr>
<tr>
<td>Missing</td>
<td>14 (42%)</td>
<td>14 (35%)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy dose (Gy) mean (SD)</td>
<td>62.8 (7.8)</td>
<td>63 (10.2)</td>
<td>62.9 (9.1)</td>
</tr>
<tr>
<td>Radiotherapy duration (wks) mean (SD)</td>
<td>6.1 (1.6)</td>
<td>6.2 (1.7)</td>
<td>6.2 (1.7)</td>
</tr>
</tbody>
</table>
Methodological concerns 2

Primary outcome measure
  – not survival
  – ? PROM... no validated outcome measure for ORN
  – ? QoL / CTCAE symptom score
  – Prevention of osteoradionecrosis
    • Textbook definition of ORN?
    • Grading?
    • Previous trials?
- 13 published classifications
- 3 versions of CTCAE
- based on retrospective case series and may be unsuitable for prospective interventional trials of ORN prevention or treatment

<table>
<thead>
<tr>
<th>Publication &amp; Year</th>
<th>Classification</th>
<th>Criteria* not met</th>
<th>Potentially suited to trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark*, 1983</td>
<td>Grade I: 30 dives of HBO was used to attain mucosa recovery</td>
<td>a,b,c</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Grade II: 10 non-responders who needed a transoral alveolar sequestrectomy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Grade III: 10 non-responders; a bone resection was needed</td>
<td></td>
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<tr>
<td></td>
<td>Grade IV: An additional 30 dives of HBO was given to patients who needed a bone graft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffin*, 1983</td>
<td>Minor: Small sequestrations that may separate spontaneously over several weeks</td>
<td>b</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Major: Bone necrosis extending to the entire thickness of the jaw; pathological fracture sometimes present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morton*, 1986</td>
<td>Minor: Bone exposure with ulceration and a history of spontaneously resolving bone sequestrations</td>
<td>b</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Moderate: Small sequestrum limited in nature and resolving spontaneously</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major: Large area of exposed bone and sequestrum; bone fracture and fistula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein*, 1987</td>
<td>Stage I: Resolved/Healed, with or without pathological fracture</td>
<td>b</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage II: Chronic/persistent non-aggressive, with or without pathological fracture</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Stage III: Active/progressive, with or without pathological fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glanzmann*, 1995</td>
<td>Stage 1: Bone exposure without signs of infection and persisting for at least 3 months</td>
<td>c</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage 2: Bone exposure with infection or sequestrum and without the signs of stage 3-5</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Stage 3: Bone necrosis treated with mandibular resection with a satisfactory result</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Stage 4: Bone necrosis with persistent problems despite mandibular resection</td>
<td></td>
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<tr>
<td></td>
<td>Stage 5: Death due to ORN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clayman*, 1997</td>
<td>Type I: Presenting with bone loss with intact gingiva or mucosa</td>
<td>b,f</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Type II: Bone exposure with secondary contamination; an aggressive infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone*, 2000</td>
<td>Stage 0: No defect detected</td>
<td>f</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage I: Radiological evidence of necrotic bone with intact mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage II: Positive radiographic findings with denuded bone intraorally</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: Exposure of the necrotic bone; skin fistula and infection</td>
<td></td>
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<tr>
<td></td>
<td>Stage IV: Superficial involvement of the mandible only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz*, 2002</td>
<td>Stage II: Localized involvement of the mandible, with or without soft tissue necrosis</td>
<td>e</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage III: Diffuse involvement of the mandible, with or without soft tissue necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notani*, 2003</td>
<td>Stage I: ORN confined to alveolar bone</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage II: ORN limited to the alveolar bone and/or above the level of the inferior alveolar canal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: ORN under the lower part of the inferior alveolar canal, with fistula or bone fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsai*, 2013</td>
<td>Stage I: Minimal bone exposure with conservative management only</td>
<td>c,e</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage II: Minor debridement required</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: HBO needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage IV: Major surgery needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karagozoglu*, 2014</td>
<td>Stage I: Bone exposure for more than 1 month; no distinct changes on imaging</td>
<td>f</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage II: Bone exposure with no distinct changes on imaging, with or without symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: Bone exposure with distinct changes on imaging, with no involvement of the lower mandible border</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage IV: Necrotic bone involving the lower border of the mandible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyons*, 2014</td>
<td>Stage 1: &gt;2.5 cm length of bone affected; asymptomatic, medical management indicated</td>
<td>c,f</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage 2: &gt;2.5 cm length of bone affected; involving fracture or the inferior dental nerve, medical management indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 3: &gt;2.5 cm length of bone affected; symptomatic, with no other features, debridement indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 4: &gt;2.5 cm length of bone affected; bone fracture and involving inferior dental nerve or fistula, flap reconstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har*, 2015</td>
<td>Stage I: Symptoms without signs other than osteodysplastic radiographic changes</td>
<td>f</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Stage 2: &gt;5 cm radiographic change with no exposure (50), intraoral or skin defect (51), both intraoral &amp; skin defect (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 3: Pathological fracture with no exposure (50), intraoral or skin defect (51), both intraoral &amp; skin defect (52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CTCAE Version [29]

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria* not met</th>
<th>Potentially suited to trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Osteonecrosis / Avascular Necrosis&quot; v2.0 1999[7]</td>
<td>Grade 0: None</td>
<td>b,c,d,e,f</td>
</tr>
<tr>
<td></td>
<td>Grade 1: Asymptomatic and detected by imaging alone</td>
<td></td>
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<tr>
<td></td>
<td>Grade 2: Symptomatic and interfering with function, but not interfering with ADL</td>
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<td></td>
<td>Grade 3: Symptomatic and interfering with ADL</td>
<td></td>
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<tr>
<td></td>
<td>Grade 4: Symptomatic or disabling</td>
<td></td>
</tr>
<tr>
<td>&quot;Osteonecrosis / Avascular Necrosis&quot; v3.0 2006[8]</td>
<td>Grade 1: Asymptomatic, radiographic findings only</td>
<td>b,c,d,e,f</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (e.g. minor sequestrum)</td>
<td></td>
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<tr>
<td></td>
<td>Grade 3: Symptomatic and interfering with ADL; operative intervention, or hyperbaric oxygen indicated</td>
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</tr>
<tr>
<td></td>
<td>Grade 4: Disabling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 5: Death</td>
<td></td>
</tr>
<tr>
<td>&quot;Osteonecrosis of jaw&quot; v.4.03 2010[9]</td>
<td>Grade 1: Asymptomatic, clinical or diagnostic observations only; intervention not indicated</td>
<td>b,c,d,e,f</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Symptomatic; medical intervention indicated (e.g. topical agents); limited instrumental ADL</td>
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<tr>
<td></td>
<td>Grade 3: Severe symptoms; self limiting care ADL; elective operative intervention indicated</td>
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<tr>
<td></td>
<td>Grade 4: Life-threatening consequences; urgent intervention indicated</td>
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<tr>
<td></td>
<td>Grade 5: Death</td>
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</tbody>
</table>
Post-irradiation dental care involving trauma to tissue can require a costly prophylactic measure.

Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin

Robert E. Marx, DDS
Robert P. Johnson, DDS
Stuart N. Kline, DDS

The pathogenesis of osteoradionecrosis has recently been shown to be a radiation-induced, nonhealing, and hypoxic wound rather than an osteomyelitis of irradiated bone.¹ Since this discovery, a scientific basis for the use of hyperbaric oxygen in the treatment phase of osteoradionecrosis has been established.²,³ The data supporting the use of hyperbaric oxygen in treatment are compelling and include a proved tissue angiogenesis,⁴ a collagen synthesis and thus wound healing enhancement,⁵ and several controlled but retrospective clinical studies.²,³,⁶ However, these studies have been concerned only with the treatment phase of osteoradionecrosis. To date, no studies related to the jaws have addressed a trial of hyperbaric oxygen in a prospective randomized fashion and none has addressed the prevention phase of osteoradionecrosis.

The purpose of this study was to test the hypothesis of whether the hyperbaric oxygen protocol currently established for soft tissue revascularization⁷ can prevent the development of osteoradionecrosis after tooth removal in a high-risk patient population.

Methods and materials

Three centers were chosen to participate in this study. These included a university training center, a private practice, and a military oral and maxillofacial surgery care facility as well as both multiple and monoplace hyperbaric oxygen delivery systems. Seventy-four patients who met the following criteria were entered into the study. Patients were included who:
- Had an indication for removal of one or more teeth in a segment of the mandible that had received a documented absorbed irradiation dose of 6,000 rads or greater.
- Agreed to maintain follow-up visits for a minimum of 6 months.
- Patients were excluded who:
  - Had received irradiation less than 6 months or more than 15 years ago.
  - Had known contraindications to penicillin or exposure to 100% oxygen at 2.4 atmospheres absolute pressure. For the most part, this included penicillin hypersensitivity, optic neuritis, and immunosuppressive drug therapy.
  - Showed evidence of persistent tumor or

Table 1  Tooth removals in bone-irradiated to dose = 6,000 rads.

|     | No. patients | No. teeth | No. ostoradio-
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>necrotized sockets</td>
</tr>
</tbody>
</table>
|     |              |           |osteoradio-
|     |              |           |necrotized |
| PCN* group | 37 | 135 | 11 (22.9%) | 11 (29.9%) |
| HBO group | 37 | 135 | 4 (2.6%) | 2 (5.7%) |

*PCN—penicillin
HBO—hyperbaric oxygen

JADA, Vol. 111, July 1985  19

- **Grade 1:** ORN confined to alveolar bone

- **Grade 1**: ORN confined to alveolar bone
- **Grade 2**: ORN alveolar bone and/or mandible above the level of inferior alveolar canal

• **Grade 1:** ORN confined to alveolar bone

• **Grade 2:** ORN alveolar bone and/or mandible above the level of inferior alveolar canal

• **Grade 3:** ORN involving the mandible below the level of inferior alveolar canal / skin fistula / pathologic #
Minor Bone Spicules
<20mm²
i.e. 4 x 5mm, 10 x 2mm
### Classification and definition of ORN in HOPON trial

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Classification</th>
<th>Clinical and radiographic findings on blinded panel review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healed</td>
<td>Mucosal Healing</td>
<td>Healed mucosa and absence of radiographic changes</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>Minor Bone Spicules</td>
<td>Exposed bone measures &lt;20mm² and in the absence of radiographic changes</td>
</tr>
<tr>
<td></td>
<td>Notani 1</td>
<td>Exposed bone &gt;= 20mm² and radiographic changes, both confined to dentoalveolar process</td>
</tr>
<tr>
<td></td>
<td>Notani 2</td>
<td>Exposed bone &gt;= 20mm² and radiographic changes beyond dentoalveolar process but above inferior dental nerve canal</td>
</tr>
<tr>
<td></td>
<td>Notani 3</td>
<td>Exposed bone &gt;= 20mm² and radiographic changes affecting the full thickness of mandible, or pathological fracture, or extra-oral fistula.</td>
</tr>
</tbody>
</table>
Refining the definition of mandibular osteoradionecrosis in clinical trials: The cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis)

Richard Shaw a,b,*, Binyam Tesfaye b, Matt Bickerstaff b, Paul Silcocks b, Christopher Butterworth a,c

a Department of Molecular and Clinical Cancer Medicine, University of Liverpool & Head & Neck Division, Aintree University Hospital NHS Foundation Trust, Liverpool L9 7AL, UK
b Cancer Research UK Liverpool Cancer Trials Unit, University of Liverpool Cancer Research Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, L69 3GL, UK
c Department of Restorative Dentistry, Liverpool University Dental Hospital, Pembroke Place, Liverpool L3 5PS, UK
Methodological concerns 3

Initially funded on feasibility basis and transition to phase 3 trial threatened momentum

• No similar trials in UK hence reluctance to fund phase III study at outset
• CRUK FSC funded with feasibility endpoints
• Phase III – assumptions were made that other recruitment centres would be found
Methodological concerns 4

- Barriers to recruitment

Barriers to recruitment for surgical trials in head and neck oncology: a survey of trial investigators

Geetinder Kaur, Iain Hutchison, Hisham Mehanna, Paula Williamson, Richard Shaw, Catrin Tudur Smith

ABSTRACT

Objectives: Many randomized trials in surgery suffer from recruitment rates that are low, with many failing to recruit the target number of patients. The aim of this study is to identify potential barriers to recruitment among head and neck cancer surgery trialists.

Design: A mixed-methods approach was used to gather data. Interviews were conducted with surgical trialists, and a questionnaire was sent to all surgeons in the National Cancer Research Network.

Setting: Secondary care and regional oncology centers.

Participants: Analyzed national data on cohort studies with a primary endpoint of surgical outcomes, focusing on the prevalence of recruitment issues identified.

Results: The most commonly identified barrier to recruitment was patient preference for one arm of the trial or to have surgery elsewhere. Some patients preferred surgery elsewhere and did not want to enter the trial. The most common strategy identified was for the co-investigator to make contact with the patient to discuss their options.

Conclusions: Our findings confirm that most surgical trials in head and neck cancer surgery suffer from recruitment issues. The most common reason for this is patient preference. However, there are several strategies that can be employed to address these issues.

INTRODUCTION

The requirement to formally exchange new innovations and technologies introduced into clinical practice and to ensure that these are safe and effective is fundamental to the ethical practice of surgery. The practice of evidence-based surgery is challenging because of several factors...
Challenges & Barriers in Trials

Trials with highest chances of failure:

- Arms of trials appear to be highly dissimilar to patients
- Treatment versus ‘no treatment’ design
- Complexity
- Time to conduct trial >3 years
- Lack of research nurse support
- Need for multiple sites per centre
- High cost of one arm of trial (excess treatment costs)
- Lack of equipoise
- Established (“old”) treatments in both or either arms
Methodological concerns 5: Excess treatment costs

- HBO costs were approx. £5k per patient in treatment arm
- Widely differing approach from PCTs / CCGs / Trusts & Specialist Commissioners
- NHS Subvention Funds
Methodological concerns 6

Control arm to Hyperbaric Oxygen / Binding

• Option for ‘Sham HBO’?
  – Costs
  – Effect of pressure / change in inspired O2
  – Will blinding truly be maintained?

• Alternative
  – Unblinded to participant and site PI
  – Primary endpoint analysis blinded by review of clinical photographs and radiographs

DAHANCA-21

- Lone Forner, DDS, PhD.
- Hyperbaric Oxygen Unit, Copenhagen University Hospital
- Blegdamsvej 9
- DK-2100 Copenhagen
- lone.forner@rh.regionh.dk
Study design

Group I: The participants of group I receive 30 preoperative HBO treatment sessions and immediately thereafter surgical removal of the necrotic bone/conservative treatment. Then, 10 postoperative HBO sessions are given. The date of the intervention is registered as the first day of the follow-up period.

Group II: The participants of group II do not receive HBO treatment, but surgery/conservative treatment as described above. The date of the intervention is registered as the first day of the follow-up period.
Primary endpoint

NCI Common Toxicity Criteria:

- Grade 1: Asymptomatic, radiographic findings only.
- Grade 2: Symptomatic and interfering with function, but not interfering with ADL (Activities of Daily Living). Minimal bone removal indicated i.e. minor sequestrectomy).
- Grade 3: Symptomatic, interfering with ADL. Operative intervention or hyperbaric oxygen indicated.
- Grade 4: Disabling
- Grade 5: Death
Secondary endpoints

- Life quality (EORTC schemes QLQ-C30, QLQ-H&N35)
- Body Mass Index
- Pain intensity (VAS)
- Analgetics consumption
- Antibiotics consumption
- Trismus
- Xerostomia
- Dysphagia
HOPON & DAHANCA21 - Conclusions

• Methodology ill defined – some progress
• Need for evidence clear with increasing clinical problem
• In retrospect, we were bound to have problems!
• Governance structures, funding, TSC & IDMC worked well but we had to ‘think on the hoof’ and adapt
• Some funding for well designed cohorts would probably be better value than only funding RCTs
• ‘Core outcome set’ for radiation toxicity would be helpful