

# Special Report

## Hyperbaric Oxygen for Chronic Tissue Radiation Injury



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### **HBO<sub>2</sub> AND RADIATION INJURY**

Radiation therapy can cause two forms of tissue injury: Acute and delayed. Acute injuries are typically self limited and treated symptomatically. The pathophysiology of delayed radiation injury is that of endarteritis with secondary tissue fibrosis and loss of capillary bed. The result is hypovascular, hypocellular, hypoxic tissue with impaired potential for repair of injury. Because radiation-induced capillary loss is progressive rather than transient, tissue breakdown in previously irradiated tissue is often chronic and nonhealing. It may occur many years after treatment.

It is known from both animal and human studies that HBO<sub>2</sub> is capable of inducing neovascularization and capillary regrowth in irradiated tissue. This property has been utilized for the treatment of osteoradionecrosis of the mandible for over three decades. Success in this area has led researchers to apply hyperbaric oxygen (HBO<sub>2</sub>) to the treatment of radiation injury in other organ systems.

HBO<sub>2</sub> is currently utilized as treatment for a variety of forms of chronic radiation injury, in both bone and soft tissue. The mechanism of benefit is thought to be similar at all sites, with stimulation of angiogenesis in the radionecrotic tissue leading to subsequent healing. Advances in the past few years have been most notable in the various forms of soft tissue radionecrosis.

### **EXPERIENCE IN TREATMENT OF BREAST AND CHEST WALL RADIONECROSIS**

Soft tissue radionecrosis of the breast or chest wall involving an open, nonhealing wound is a routine indication for hyperbaric oxygen therapy. In a systematic literature review, 74 published studies that utilized HBO<sub>2</sub> to treat a variety of radiation-injured tissues were summarized.<sup>1</sup> All but 7 demonstrated that HBO<sub>2</sub> was effective in treating the tissues involved, including those publications reporting series of patients treated for breast or chest wall radionecrosis. The mechanism by which radiated-tissue regeneration occurs with HBO<sub>2</sub> is generally thought to be neovascularization, regardless of the site. With regard to breast or chest wall radionecrosis specifically, the authors gave HBO<sub>2</sub> treatment for the indication an American Heart Association Class IIb designation “Acceptable and Useful Therapy Based on Fair to Good Evidence.”

In patients with breast or chest wall radiation necrosis, HBO<sub>2</sub> is used either to primarily heal the chronic wound or to prepare the site for surgical coverage or closure. At Virginia Mason, we

recommend an initial course of 40 HBO<sub>2</sub> treatments when the wound is small and the goal is healing by secondary intention. In larger wounds that will likely require eventual skin grafting or flap closure, 20–30 preoperative treatments are typically administered. In response to the angiogenesis stimulated, granulation and wound quality improve, often converting a non-graftable wound to one that can be successfully closed. Because the angiogenesis stimulated by preoperative HBO<sub>2</sub> treatment does not restore tissue capillary density to a completely normal level, the tissue is still relatively hypoperfused. To compensate for this, 10 postoperative treatments are typically administered to provide oxygen and promote healing.

### **Elective Breast Surgery Following Radiation Therapy**

After undergoing conservative surgery and radiation therapy for breast cancer, some women eventually desire elective reduction mammoplasty or breast reconstructive surgery. Postoperative healing complications in previously irradiated tissue have been well described in the literature. For example, in a large study at the University of Miami, patients requiring head and neck flap surgery in previously irradiated fields demonstrated a significantly lower incidence of postoperative wound dehiscence (11% vs. 48%) and wound infection (6% vs. 24%) when perioperative HBO<sub>2</sub> was administered.<sup>2</sup>

At Virginia Mason, we have adopted this approach for selected patients undergoing elective surgery in irradiated breast tissue. In coordination with physicians in the VM Section of Plastic and Reconstructive Surgery, patients are given 20 preoperative HBO<sub>2</sub> treatments to stimulate angiogenesis and improve perfusion in the irradiated breast. Following surgery, they return to the Center for Hyperbaric Medicine and receive postoperative therapy, typically 10 treatments or until the surgeon judges that the wounds are likely to heal without complication. Our experience in this area was recently published in *Plastic and Reconstructive Surgery*.<sup>3</sup> Among women with a history of unilateral breast irradiation undergoing bilateral reduction mammoplasty, results were cosmetically equivalent between breasts when adjunctive hyperbaric oxygen therapy was utilized.

### **Hyperbaric Treatment of Chronic Breast Symptoms following Radiation Therapy**

In a study from Germany, outcomes of 44 patients suffering from chronic complications following lumpectomy and radiation therapy for early breast cancers were reported.<sup>4</sup> The patients had various combinations of pain, edema, telangiectasias, and fibrosis. Symptom severity was assessed using a modified SOMA-LENT scoring system. Each patient was assigned a score from 0–4 for severity of symptoms in the categories of pain, edema, fat necrosis/fibrosis, and telangiectasia/erythema. Only

patients with Grade 3 pain (persistent and intense) or a summed score of 8 or greater were studied.

Thirty-two patients agreed to undergo hyperbaric treatment while 12 refused HBO<sub>2</sub> and constituted the control group. Women who received HBO<sub>2</sub> had a statistically significant decrease in SOMA-LENT scores compared to those who did not undergo the treatment, primarily due to reductions in pain, edema, and erythema scores. Fibrosis and telangiectasia were not reduced. Women in the control group continued to have symptoms with no improvement in pain or edema. Seven women in the HBO<sub>2</sub> group had complete resolution of their symptoms.

It is interesting to note that these patients had chronic signs and symptoms without classic radionecrosis as manifested by an open wound. It is unknown whether the mechanism of action in such cases is stimulation of angiogenesis, as is thought to be the case in usual radiation necrosis. Reduction in pain could theoretically be attributed to a placebo response to hyperbaric treatment since the study was not blinded, but severity of edema and erythema were objectively graded and also improved. We have treated several such patients at Virginia Mason over the past few years with similar positive outcomes.

### **EXPERIENCE IN HBO<sub>2</sub> TREATMENT OF GASTROINTESTINAL RADIATION INJURY**

Chronic radiation enteritis occurs in 5% to 20% of patients treated with abdominal or pelvic radiation. Manifestations of chronic radiation enteritis include bleeding, ulcerations, fistulas, strictures, and intestinal obstruction. The peak incidence is between 6 and 24 months following radiation exposure, but symptoms may be delayed as long as 20 years. Severe chronic proctitis is reported in 2% to 5% of patients after pelvic irradiation.

In an evidence-based review,<sup>1</sup> results from 9 published case series of patients with chronic gastrointestinal radiation injury were reviewed. Of the 114 patients reported, 36% resolved and 60% improved. The results were so consistent that the authors gave the treatment for the indication an American Heart Association Class IIa designation “Acceptable and Useful Therapy.”

### **Virginia Mason Experience Treating Gastrointestinal Radiation Injury**

At Virginia Mason, we have treated over 100 patients for gastrointestinal radiation injury. When we published our experience after the initial 65 cases, patients averaged 65 years of age and had a 9-month median duration of symptoms (range 1 to 168 months).<sup>5</sup> Bleeding was the primary indication for HBO<sub>2</sub> (83%), usually due to radiation proctitis. The overall response rate was 68%, with complete and partial response rates of 43% and 25%, respectively. Responses did not differ

significantly whether the treatment was for bleeding or a non-bleeding indication, or whether the radiation injury was located proximally or distally in the gastrointestinal tract. Rectal wall ulceration following radiation for prostate cancer is a more refractory problem.<sup>6</sup> Among patients we have treated, approximately 20% demonstrate complete healing on repeat endoscopic examination and 30% significantly improve. However, even for those patients who do require subsequent surgery, the angiogenesis stimulated by the course of HBO<sub>2</sub> is felt to provide advantage with regard to postoperative healing of irradiated tissues.

A recently published double-blind, prospective, controlled trial randomizing patients with radiation proctitis to hyperbaric oxygen treatment or sham hyperbaric treatments was positive, achieving healing or significant improvement in 89% of the HBO<sub>2</sub> group and 62% in the sham group (p = 0.0009).<sup>7</sup>

### **Gastrointestinal Radiation Injury: Case Presentation with Discussion**

**Case** — *The patient was a 64-year-old male diagnosed with prostate cancer 2 years earlier and treated with external beam radiation therapy. He did well for 6 months following radiation and then developed rectal bleeding. Bleeding was initially intermittent but progressed to 3–4 times weekly. Endoscopy demonstrated friable rectal mucosa with numerous telangiectasias and oozing, consistent with diffuse changes of radiation proctitis. Argon plasma coagulation was performed on one occasion without symptomatic benefit.*

**Discussion** — The presumed mechanism for healing radiation injury to the rectum with hyperbaric oxygen is stimulation of capillary regrowth in the radiation-injured tissue. On average, maximal angiogenesis is believed to occur after approximately 30 HBO<sub>2</sub> treatments. We have shown that a hyperbaric treatment course of fewer than 30 treatments is associated with a reduced likelihood for healing in soft-tissue radionecrosis of the GI tract.<sup>8</sup> In an analysis of published series of patients with bladder radionecrosis, investigators at Duke University found that 30 or 40 hyperbaric treatments were equally effective for acute resolution of symptoms.<sup>9</sup> However, long-term durability of the result was better when 40 treatments are administered.

At Virginia Mason, we recommend an initial treatment course of 40 HBO<sub>2</sub> treatments for all forms of soft-tissue radionecrosis. In the case of radiation proctitis, patients should have undergone a recent endoscopic evaluation to confirm the etiology of their rectal hemorrhage and to obtain baseline photo documentation of the severity of their radiation injury.

**Case (cont.)** — *The patient received 40 outpatient hyperbaric treatments over 8 weeks, resulting in an estimated 80% reduction in bleeding severity. Repeat sigmoidoscopy*

*demonstrated improvement in the rectal mucosa with fewer telangiectasias, less friability, and no bleeding.*

**Discussion** — In such a case, we will typically stop treatment at this point, as many patients continue to improve after HBO<sub>2</sub> is discontinued, once healing has been initiated. If symptoms continue to be significantly bothersome, the patient's treatment course can be extended another 20 treatments, to a maximum of 60.

### **EXPERIENCE IN HBO<sub>2</sub> TREATMENT OF RADIATION CYSTITIS**

Chronic radiation cystitis occurs in 1% to 5% of patients treated with radiation therapy for pelvic malignancy, such as prostate cancer. Such bladder injury results in pain, urinary frequency, and chronic hematuria. Urinary bleeding can cause recurrent obstruction, and may render the patient transfusion dependent.

In an evidence-based review,<sup>1</sup> results from 190 patients reported in 17 publications were reviewed. When combined, the response rate to a course of hyperbaric treatment was 76%. The results were so consistent that the authors gave the treatment for the indication an American Heart Association Class IIa designation "Acceptable and Useful Therapy."

### **Virginia Mason Experience Treating Radiation Cystitis**

At Virginia Mason, we have treated over 100 patients for hemorrhagic radiation cystitis, the largest reported series in the world. When we published our experience after the first 62 cases, patients in the series averaged 70 years of age and had a median delay between completion of radiation therapy and onset of urinary hemorrhage of 24 months.<sup>10</sup> The overall response rate with regard to hematuria was 86% (complete response 37%; partial response 49%). Among 22 patients undergoing cystoscopy both before and after treatment, cystoscopic appearance improved in 77%.

### **Is Early HBO<sub>2</sub> More Effective in Treatment of Radiation Cystitis?**

We have also examined the response rate with regard to timing of hyperbaric therapy. When treated within 6 months of hematuria onset, 96% of patients had complete or partial symptomatic resolution, as compared to 66% when treatment was initiated longer than 6 months after the onset of hematuria.<sup>11</sup>

### **Radiation Cystitis: Case Presentation with Discussion**

**Case** — *The patient was a 75-year-old male retired pipe fitter, diagnosed with clinical stage T2 prostate cancer 3 years earlier. Treatment with combined external beam plus brachytherapy*

seed radiation therapy resulted in a PSA decline from 5.6 to 0.3, which was sustained. He did well for 2 years following radiation, and then developed hematuria. Bleeding was initially intermittent, but progressed to continuous after two months and was occasionally associated with the passage of clots. Cystoscopy demonstrated diffuse changes of radiation cystitis. Fulguration was performed on one occasion, without symptomatic benefit.

**Discussion** — The presumed mechanism for healing of radiation injury to the bladder by hyperbaric oxygen is stimulation of capillary regrowth in the radiation-injured tissue. On average, maximal angiogenesis is believed to occur after approximately 30 HBO<sub>2</sub> treatments. It has been shown that a hyperbaric treatment course of fewer than 30 treatments is associated with a reduced likelihood for healing in radiation cystitis.<sup>8</sup> In an analysis of published patient series, investigators at Duke University found that 30 or 40 hyperbaric treatments were equally effective for acute resolution of symptoms.<sup>9</sup> However, long-term durability of the result is better when 40 treatments are administered.

At Virginia Mason, we recommend an initial treatment course of 40 HBO<sub>2</sub> treatments. Patients should have undergone a recent cystoscopy to exclude malignancy as the etiology of their urinary hemorrhage and to obtain baseline documentation of the severity of their radiation injury.

**Case (cont.)** — *The patient received 40 outpatient hyperbaric treatments over 6 weeks, resulting in an estimated 80% reduction in bleeding severity. Repeat cystoscopy per protocol demonstrated improvement in the bladder mucosa but not complete healing.*

**Discussion** — After 40 treatments, cystoscopy is repeated to assess response and provide a new baseline for future comparison. If the bladder is healed, hyperbaric therapy is discontinued. If it appears improved but incompletely healed, the patient's treatment course can be extended another 20 treatments, to a maximum of 60. This extension of treatment can be continuous with the initial therapeutic course, or after a break to allow the patient some time off. Regression of healing does not occur after such a break.

**Case (cont.)** — *Following a 3-week vacation, the patient returned and completed an additional 20 HBO<sub>2</sub> treatments. At the end of this series, he noted only rare intermittent hematuria and was quite pleased with the result.*

**Discussion** — After healing with an initial course of hyperbaric therapy, a small percentage of patients recur in 3 to 10 years. A second course of HBO<sub>2</sub> treatments can be administered. In our experience, re-treatment is associated with a 66% response rate, in contrast to 86% response with initial treatment.<sup>10</sup>

## DOES HYPERBARIC OXYGEN ENHANCE CANCER GROWTH OR RECURRENCE?

It is sometimes asked whether exposure to high pressure oxygen will increase the likelihood of recurrence or enhance growth in an occult cancer, due to concern that HBO<sub>2</sub> might stimulate angiogenesis in tumors. There are extensive published data from both animal models and clinical experience.<sup>12</sup> The vast majority of studies show no enhancement of cancer recurrence or growth. Recent animal models showing no enhanced growth of the cancers under study include transplanted human prostate cancer cells, tumor cells in culture, chemically-induced murine mammary tumors, xenografts of human head and neck cancers transplanted into experimental animals, and murine colorectal cancer cells transplanted to cause liver metastases.

## CONCLUSIONS

Over the last several years, increasing amounts of evidence have been compiled demonstrating the effectiveness of hyperbaric oxygen therapy for treatment of chronic soft tissue radiation injury. Since these injuries can cause severe morbidity and are often untreatable by any other means, hyperbaric oxygen offers a therapeutic opportunity for many afflicted patients, some who have suffered with the problem for years.

## HOW TO REFER PATIENTS

To make an appointment or for more information, please call Neil Hampson, MD, at (206) 583-6543 or e-mail him at Neil.Hampson@vmmc.org. You also can contact us by calling the Regional Clinician Service Center at (877) 333-0122, faxing us at (800) 641-9002, or e-mailing us at referral@vmmc.org, Monday through Friday, 8 a.m. to 5 p.m.

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