

## HYPERBARIC OXYGEN THERAPY FOR RADIATION-INDUCED HEMORRHAGIC CYSTITIS

DIANE M. NORKOOL, NEIL B. HAMPSON, ROBERT P. GIBBONS AND ROBERT M. WEISSMAN

*From the Hyperbaric Department, Virginia Mason Hospital, and Sections of Pulmonary and Critical Care Medicine, Urology and Renal Transplantation, Virginia Mason Clinic, Seattle, Washington*

### ABSTRACT

From May 1988 through May 1991, 14 patients with radiation-induced hemorrhagic cystitis confirmed by cystoscopy and biopsy, who had failed all other attempts at management and who had no evidence of infection or recurrent malignancy, were treated with hyperbaric oxygen therapy. During followup ranging from 10 to 42 months 8 patients (57%) had complete resolution of symptoms and 2 (14%) had marked improvement, for a total of 10 patients (71%) with a positive outcome. Of 4 patients (29%) with a poor outcome 3 had limited improvement and were later diagnosed as having recurrent malignancy that was not present on biopsy before hyperbaric treatment. One patient was withdrawn from hyperbaric treatment due to illness. The average cost per patient was \$10,000 to \$15,000, comparing favorably to the cost of multiple conservative treatments to control symptoms. Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis appears to be an efficacious treatment modality for patients who have failed other forms of management.

KEY WORDS: bladder diseases, cystitis, radiation injuries, hyperbaric oxygenation

Injury to the bladder is an unfortunate side effect of therapeutic radiation administered for a variety of pelvic malignancies. Radiation-induced hemorrhagic cystitis is often a troublesome problem for the patient and physician. Significant symptoms typically include recurrent hemorrhage, urinary urgency and pain. Large studies report that 5.7 to 11.5% of the patients treated with pelvic radiation have bladder complications.<sup>1-3</sup> Microscopic examination of bladder biopsies most commonly reveals mucosal edema, vascular telangiectasias, obliterative endarteritis and smooth muscle fibrosis.<sup>4</sup> Such fibrosis may result in diminished bladder capacity.

Radiation-induced hemorrhagic cystitis is usually a progressive disease that will not resolve spontaneously in the advanced stages. Various palliative treatments, including instillation of alum, silver nitrate and formalin, are commonly used to control bleeding. Systemic medications, such as aminocaproic acid, an inhibitor of fibrinolysis, have also been used. These procedures are aimed at treating symptoms but they do nothing to promote healing. Surgical cauterization and hypogastric artery ligation have provided only limited success. Many patients are ultimately left with a contracted, noncompliant and chronically infected bladder requiring cutaneous ureterostomy or cystectomy with urinary diversion.<sup>4</sup>

### METHODS

From May 1988 through May 1991, 14 patients with radiation-induced hemorrhagic cystitis confirmed by cystoscopy and biopsy who had failed all other attempts at management and who had no evidence of infection or recurrent malignancy were treated with hyperbaric oxygen therapy at the Virginia Mason Hospital hyperbaric department in Seattle, Washington. There were 12 male and 2 female patients between 15 and 85 years old (mean 62). Patients received 100% oxygen in a multiplace hyperbaric chamber at a pressure of 2.4 atmospheres absolute for 90 minutes 5 to 6 days per week for an average of 28 treatments (range 9 to 58). Criteria for patient evaluation were the presence or absence of hematuria, urgency and pain. Data were collected from medical records and telephone interviews.

### RESULTS

Of the 14 patients 8 (57%) experienced complete resolution of the symptoms (table 1). Two patients within this group also

had symptoms of radiation proctitis and these symptoms resolved within 1 to 2 weeks (8 to 12 treatments) of initiating hyperbaric oxygen therapy. Some patients continued to have microscopic hematuria on urinalysis and/or other minor symptoms (pain, urgency and frequency) after completing the hyperbaric oxygen treatments. However, these symptoms resolved within several months, suggesting that healing continued despite the discontinuation of hyperbaric oxygen.

Two patients achieving complete resolution of symptoms underwent cystoscopy and fulguration of bleeding sites in addition to hyperbaric oxygen. Both patients also underwent this procedure before hyperbaric oxygen treatment without success in stopping the bleeding. One patient was hospitalized for severe hematuria 26 days after quitting hyperbaric oxygen because of claustrophobia (he had received 10 hyperbaric oxygen treatments). Following cystoscopy and fulguration, the bleeding decreased significantly and he was symptom-free 2 months later. The other patient who underwent cystoscopy and fulguration following hyperbaric oxygen was a 69-year-old woman who had received 6,300 cGy. of radiation for bladder cancer and had the most severe symptoms among our patients. She was experiencing gross hematuria complicated by chronic anticoagulation with warfarin for a prosthetic mitral valve. For several months before hyperbaric oxygen treatment she had required weekly transfusions with 3 units of packed red blood cells to maintain the hematocrit at 21 to 28%. After 30 hyperbaric oxygen treatments she continued to experience significant hematuria. Cystoscopy and fulguration of several bleeding sites were done, following which no additional bleeding was noted. The urologist noted that the appearance of the bladder wall had significantly improved since initiating hyperbaric oxygen. This patient completed 10 additional hyperbaric oxygen treatments (40 total) and has required no additional transfusions during the subsequent 3½ years.

Two patients (14%) achieved significant improvement in the symptoms (table 2). When combined with the 8 patients who experienced total resolution of symptoms, 71% of our patients responded favorably. One patient in the improved group was a 65-year-old insulin-dependent diabetic who received 6,600 cGy. radiation for bladder and prostate cancer. He was symptom-free for 17 months after receiving 30 hyperbaric oxygen treatments. Gross hematuria then developed requiring several hospitalizations and blood transfusions. The condition was com-

TABLE 1. *Patients with resolution of symptoms*

Sex—Age	Ca Radiated	Dose (cGy.)	No. Hyperbaric Oxygen Treatments	Results*	Followup (mos.)
F—69	Bladder	6,300	40 plus cystoscopy†	Hematuria resolved, urgency with occasional dribbling	42
M—74	Prostate	7,020	20	Hematuria and urgency resolved, pain with occasional burning	38
M—19	Pelvic Ewing's sarcoma	5,580	30	Hematuria and urgency resolved	31
M—80	Bladder	6,750	18	Hematuria, urgency and proctitis symptoms resolved	24
M—63	Prostate	4,500	24	Hematuria and urgency resolved	19
M—66	Prostate	6,760	30	Hematuria and urgency resolved	18
M—70	Prostate	6,500	10 plus cystoscopy† (quit hyperbaric oxygen)	Hematuria resolved	15
M—75	Prostate	5,940	30	Hematuria with rare small clots, urgency and proctitis symptoms resolved	11

\* If symptom is not listed it was not present before hyperbaric oxygen treatment.

† Required cystoscopy with fulguration of isolated bleeding sites.

TABLE 2. *Patients with improvement in symptoms*

Sex—Age	Ca Radiated	Dose (cGy.)	No. Hyperbaric Oxygen Treatments	Results*	Followup (mos.)
M—15	Pelvic rhabdomyosarcoma	10,000	30	Hematuria reduced, urgency and pain resolved	30
M—65	Prostate, bladder	6,660	30	No hematuria for 17 mos., urgency and pain resolved	29 (cystectomy for recurrent hemorrhage)

\* If symptom is not listed it was not present before hyperbaric oxygen treatment.

TABLE 3. *Patients who failed hyperbaric oxygen treatment*

Sex—Age	Ca Radiated	Dose (cGy.)	No. Hyperbaric Oxygen Treatments	Results*	Followup (mos.)
F—43	Uterus, rectum, ovary	8,800 plus implants	9 (withdrawn)	Persistent hematuria, urgency (catheter), severe pain	Died of sepsis (1)
M—73	Prostate	6,480	33	Decreased hematuria, urgency (incontinent), decreased pain (enteritis symptoms improved)	Urinary diversion (1)
			(hyperbaric oxygen resumed after 9-mo. interval) 25	Increased hematuria, urgency (diversion), increased pain	Died of recurrent Ca (25)
M—65	Bladder	5,600	30	Hematuria improved, severe urgency, mild pain	Cystectomy for recurrent Ca (32)
M—85	Bladder, prostate	6,660	22 (quit hyperbaric oxygen)	Hematuria resolved for 2 mos., then increased, urgency (incontinent), pain resolved	Cystectomy for recurrent Ca (10)

\* If symptom is not listed it was not present before hyperbaric oxygen treatment.

plicated by other medical problems and he chose to undergo cystectomy. The pathology report revealed several ulcerated areas within the bladder but no evidence of malignancy.

Four patients (29%) in the study were classified as having poor outcomes (table 3). A 43-year-old woman received 9 hyperbaric oxygen treatments, and was then withdrawn from treatment due to severe hemorrhage and sepsis. The remaining 3 patients initially improved with hyperbaric oxygen (decreased hematuria and decreased pain) but underwent cystectomy several months after hyperbaric oxygen treatment because of persistent incontinence and recurrent hematuria. Pathology reports from cystectomy showed the presence of cancer in all 3 patients despite negative biopsies during cystoscopy just before initiating hyperbaric oxygen treatment.

#### DISCUSSION

Radiation-induced tissue injury is the result of progressive endarteritis leading to hypovascular, hypocellular and hypoxic tissue. The ability to replace normal collagen and cellular loss is compromised, resulting in tissue breakdown. Once irradiated tissue breaks down, it is unlikely that healing will occur.<sup>5</sup>

Hyperbaric oxygen therapy has been found to enhance healing in a variety of radiation-injured tissues.<sup>6-8</sup> In a recent animal model, breathing 100% oxygen at normal atmospheric pressure produced no effect on angiogenesis in irradiated tissues.<sup>8</sup> However, hyperbaric oxygen produced an 8 to 9-fold increase in vascular density in irradiated tissues over normobaric oxygen

and air-breathing controls, while simultaneously raising transcutaneous oxygen levels to within 85% of normal. This stimulus for angiogenesis appears to be mediated through tissue macrophages responding to the steep oxygen gradient achieved in the hyperbaric environment.<sup>9</sup> Long-term followup for as much as 4 years after hyperbaric oxygen therapy has revealed that transcutaneous oxygen measurements remain near normal levels, implying that the angiogenesis is essentially permanent.<sup>10</sup>

In our study of 14 patients with radiation-induced hemorrhagic cystitis 71% achieved complete resolution of symptoms or experienced significant improvement. In an earlier study by Weiss and Neville at Temple University 7 of 8 patients (88%) treated with hyperbaric oxygen for radiation-induced hemorrhagic cystitis healed or were significantly improved.<sup>11</sup> In a similar study by Rijkman et al from Amsterdam 6 of 10 patients (60%) achieved similar results.<sup>12</sup>

Two patients required cystoscopy and fulguration of bleeding sites in addition to hyperbaric oxygen. While hyperbaric oxygen is able to promote healing of bladder mucosa, some larger areas of erosion over vessels may cause persistent bleeding. Fulguration of these lesions may be helpful. Fulguration before the institution of hyperbaric oxygen, however, was not successful in these patients.

In our study few side effects from hyperbaric oxygen treatment were noted. Significant hyperbaric-induced myopia developed in 1 patient but this is a rare occurrence. Five patients (36%) experienced mild visual changes that resolved after hy-

perbaric oxygen treatment was completed. One patient terminated the treatments due to claustrophobia but achieved resolution of symptoms despite the abbreviated course of therapy. Four patients (29%) experienced mild symptoms of ear "squeeze" (difficulty equalizing middle ear pressure), which resolved after several days. No patient experienced symptoms of central nervous system or pulmonary oxygen toxicity.

The average cost per patient in our study was \$10,000 to \$15,000, which compares favorably to the cost of multiple conservative treatments to control symptoms. These conservative treatments are aimed at controlling bleeding but they often leave patients with a contracted bladder, urinary urgency, frequency and incontinence. Overall, hyperbaric oxygen appears to be an efficacious and economical approach to the treatment of radiation-induced hemorrhagic cystitis, and it is the only therapy that has been demonstrated to promote healing in this condition. Earlier use of hyperbaric oxygen treatment should be considered before repeated instillations of chemicals that may leave the bladder fibrotic, contracted and noncompliant.

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