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EARLY HYPERBARIC OXYGEN THERAPY IMPROVES OUTCOME FOR RADIATION-INDUCED HEMORRHAGIC CYSTITIS

KIAN TAI CHONG, NEIL B. HAMPSON, AND JOHN M. CORMAN

ABSTRACT

Objectives. To assess the clinical factors that affect the efficacy of hyperbaric oxygen (HBO_2) therapy in treating radiation-induced hemorrhagic cystitis. HBO_2 therapy is an effective treatment for radiation-induced hemorrhagic cystitis, with reported response rates ranging from 76% to 100%.

Methods. The data from patients with radiation-induced hemorrhagic cystitis treated at our institution between May 1988 and December 2001 were reviewed retrospectively. All patients received HBO_2 therapy at 2.36 atm absolute pressure, with 90 minutes of 100% oxygen breathing per treatment. The outcome was assessed after at least 12 months of follow-up. We evaluated patient demographics, types of pelvic malignancy and radiotherapy, total radiation dose, onset and severity of hematuria, and prior intravesical management. Clinical improvement was defined as the absence of, or reduction in, macroscopic hematuria.

Results. A total of 60 patients (55 men and 5 women), mean age 70 years, received an average of 33 HBO_2 treatments (range 9 to 63). Of the 60 patients, 48 (80%) had either total or partial resolution of hematuria. When treated within 6 months of hematuria onset, 96% (27 of 28) had complete or partial symptomatic resolution ($P = 0.003$). All 11 patients with previous clot retention had clinical improvement if treated within 6 months of hematuria onset ($P = 0.007$). Prior intravesical chemical instillation did not affect the clinical outcome. Patients who had undergone primary, adjuvant, or salvage external beam pelvic radiotherapy showed response rates of 81%, 83%, and 78%, respectively ($P = 0.950$).

Conclusions. Our results show that delivery of HBO_2 therapy within 6 months of hematuria onset is associated with a greater therapeutic response rate. Treatment efficacy was independent of prior intravesical therapy and the timing of radiotherapy. UROLOGY **65:** 649–653, 2005. © 2005 Elsevier Inc.

Pelvic radiotherapy causes chronic fibrosis and progressive endarteritis in poorly oxygenated bladder submucosal and muscular tissues, with eventual tissue scarring. This can potentially lead to bladder mucosal sloughing and symptomatic hemorrhagic cystitis. Delayed radiation-induced hemorrhagic cystitis (HC) may appear more than 10 years after pelvic radiotherapy.[1,2] The severity of hematuria has been classified,[2] and the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) scoring criteria are commonly used in clinical trials to describe acute or late radiotherapy-related morbidities (Table I). Significant symptomatic grade 3 or 4 hematuria occurs in 2.1% to 8.2% of patients after external beam pelvic radiotherapy or brachytherapy.[3–7]

Hyperbaric oxygen (HBO_2) improves regional tissue oxygenation in previously irradiated tissue, resulting in neovascularization and capillary growth into hypoxic and scarred submucosal tissue. After HBO_2 therapy, 76% to 100% of reported patients with radiation-induced HC experienced a reduction or complete resolution of hematuria.[1,8–10] In this study, we assessed the clinical factors that may correlate with the effectiveness of HBO_2 in treating radiation-induced HC.

MATERIAL AND METHODS

The data of patients treated with HBO_2 for radiation-induced HC at our institution between May 1988 and December

From the Section of Urology and Renal Transplantation and Center for Hyperbaric Medicine, Virginia Mason Medical Center, Seattle, Washington

Reprint requests: John M. Corman, M.D., Section of Urology and Renal Transplantation, Virginia Mason Medical Center, C7-URO, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98111. E-mail: urojmc@vmmc.org

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TABLE I. *Classification of hematuria events for both acute and late radiation morbidity scoring criteria for radiation-induced hemorrhagic cystitis*

Hematuria Morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute (RTOG)	NA	NA	Gross hematuria with or without clot passage	Hematuria requiring transfusion	Death from uncontrolled hematuria
Late (RTOG/EORTC)	Minor telangiectasia (microscopic hematuria)	Generalized telangiectasia (macroscopic hematuria)	Severe generalized telangiectasia (frequent macroscopic hematuria)	Severe hemorrhagic cystitis	Death from uncontrolled hematuria

KEY: RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.
Acute morbidity defined as treatment-related complications occurring within 90 days from first radiotherapy session.

2001 were retrospectively reviewed. All patients had negative urine cultures and underwent pretreatment cystoscopic evaluation to exclude bladder malignancy and to document the presence of radiation cystitis.

Patients received HBO_2 therapy in a multiplace hyperbaric chamber with 90 minutes of 100% oxygen breathing at 2.36 atm absolute pressure per session, including 5-minute air breaks after every 30 minutes of oxygen. An initial course of 40 treatments was planned, one session daily, five times per week. The number of sessions was reduced if a patient developed nonreversible side effects or unrelated medical problems or declined further therapy. After completing 40 sessions, another 15 to 20 sessions were sometimes administered if the hematuria persisted. The data were analyzed for patients with at least 12 months of follow-up.

We evaluated the patient characteristics, primary pelvic malignancy type, modality of radiotherapy, onset and severity of symptomatic hematuria using the RTOG/EORTC criteria, time from hematuria onset to the initiation of HBO_2 treatment, and prior intravesical management. The onset of hematuria was defined as the first episode of hematuria after the initiation of pelvic radiotherapy, independent of its RTOG/EORTC grade.

The clinical outcome measures after HBO_2 therapy included symptomatic assessment (either complete resolution, partial resolution, no change, or worsening hematuria) by physicians or as reported by the patients by way of returned postal survey forms.

Clinical improvement was defined as complete or partial resolution of macroscopic hematuria. Complete resolution referred to the absence of macroscopic hematuria. Partial resolution referred to a reduction in the severity or frequency of macroscopic hematuria that corresponded to a change to a lower RTOG/EORTC grade of radiotherapy-related hematuria.

The results of the post-treatment cystoscopic evaluation were not evaluated because most patients with symptomatic improvement did not undergo repeat cystoscopy to document the absence or reduction of bladder mucosal telangiectasia or petechiae. Microscopic examination of urine was not evaluated because some patients were followed up by postal outcomes surveys without returning to the clinician's office.

The total radiation dose delivered during pelvic radiotherapy was analyzed independent of the timing of therapy (primary, adjuvant, or salvage treatment).

The data were analyzed using Statistical Package for Social Sciences, version 11.0, with the one-sided Fisher's exact test in two by two tables and the two-sided Pearson chi-square test with two degrees of freedom in the three by two table. Statistical significance was reached at a P value of 0.05 or less.

RESULTS

A total of 60 patients (55 men and 5 women) with a mean age of 70 years (range 15 to 88) received an average of 33 HBO_2 treatments (range 9 to 63). Patients with complete resolution, partial resolution, no change, and worsened hematuria had an increasing mean age of 69, 70, 75, and 80 years, respectively. Of the 60 patients, 44 men and 4 women (80%) had either complete or partial resolution of macroscopic hematuria (Table II). In our series, the most common indication for pelvic radiotherapy was prostate cancer in 50 (83%) of the 60 patients. Of this subgroup, 76% improved with HBO_2 therapy.

TABLE II. *Patient characteristics, including pelvic malignancy type, and outcome of hematuria after completing hyperbaric oxygen therapy*

Patient Characteristics	Outcome				
	Complete Resolution	Partial Resolution	No Change	Worsened	Unknown
Sex (n)					
Male (n = 55)	18	26	8	2	1*
Female (n = 5)	3	1	0	0	1†
Age (yr)					
Mean	69	70	75	80	57
Range	19–87	15–86	66–88	74–85	43–70
Pelvic malignancy (n)					
Prostate (n = 49)	25	13	8	2	1*
Bladder (n = 6)	5	1	0	0	0
Cervix (n = 2)	2	0	0	0	0
Ovarian (n = 1)	0	0	0	0	1†
Ewing's sarcoma of pubis (n = 1)	1	0	0	0	0
Pelvic rhabdomyosarcoma (n = 1)	0	1	0	0	0
History of hematuria (n)					
With clots (n = 44)	14	21	6	2	1*
With clots, no retention (n = 19)	8	9	2	0	0
With clot retention (n = 25)	6	12	4	2	1*

* *Patient drop-out owing to persistent claustrophobia.*
† *Bed-bound patient with life-threatening sacral wound septicemia.*

TABLE III. *Factors affecting therapeutic outcome of hyperbaric oxygen therapy according to lag time between onset of hematuria and first session of HBO_2 therapy*

Lag Time to HBO_2 Therapy	Complete or Partial Resolution of Hematuria (n)	Hematuria Remained Unchanged, Worsened, or Unknown (n)	*P* Value
All patients (n = 60)			
≤6 mo (n = 28)	27 (96)	1 (4)	
>6 mo (n = 32)	21 (66)	11 (34)	0.003*
Patients with history of clot retention (n = 25)			
≤6 mo (n = 11)	11 (100)	0	
>6 mo (n = 14)	7 (50)	7 (50)	0.007*

KEY: HBO_2 = *hyperbaric oxygen.*
Data in parentheses are percentages.
* *One-sided Fisher's exact test.*

Of the 60 patients, 44 had significant hematuria with clots, of whom 25 developed clot retention. After HBO_2 therapy, complete or partial resolution of hematuria was seen in 35 (80%) of the 44 with who had clots, with or without clot retention, and in 18 (72%) of the 25 patients with a history of clot retention.

HBO_2 therapy delivered within 6 months of the onset of symptomatic hematuria was associated with a 96% rate of overall clinical improvement (Table III). Patients who had treatment initiated longer than 6 months after the onset of hematuria demonstrated a significantly lower response rate at 66% ($P = 0.003$). All 11 patients with a history of clot retention who were treated within 6 months of hematuria onset had complete or partial resolution of hematuria. Of the 14 patients with prior clot retention who were treated longer than 6 months after the onset of hematuria, only 7 (50%) had a positive response to HBO_2 therapy ($P = 0.007$).

Before initiating HBO_2 therapy for ongoing hematuria, all patients underwent at least one cystoscopy with cauterization. Twelve patients received pre-HBO_2 intravesical astringent instillation with alum, silver nitrate, or formalin (Table IV). These intravesical therapies did not affect the eventual clinical response to HBO_2 ($P = 0.552$).

Patients who had undergone primary, adjuvant, or salvage external beam pelvic radiotherapy had similar clinical improvement rates at 81%, 83%, and 78%, respectively ($P = 0.950$). In patients who had received a total pelvic radiation dose of less than 6000 cGy (n = 3), between 6001 and 7000 cGy (n = 21), or greater than 7000 cGy (n = 5), complete or partial resolution of hematuria occurred in 67%, 71%, and 80%, respectively.

TABLE IV. *Clinical outcome according to prior intravesical therapy and timing of radiotherapy before HBO_2 therapy*

Therapy Type	Complete or Partial Resolution of Hematuria (n)	Hematuria Remained Unchanged, Worsened, or Unknown (n)	*P* Value
Intravesical therapy (n = 60)			
Cauterization alone (n = 48)	38 (79)	10 (21)	
Alum, silver nitrate, or formalin instillation (n = 12)	10 (83)	2 (17)	0.552*
Pelvic radiotherapy timing (n = 58)			
Primary (n = 37)	30 (81)	7 (19)	
Adjuvant (n = 12)	10 (83)	2 (17)	
Salvage (n = 9)	7 (78)	2 (22)	0.950†

KEY: HBO_2 = hyperbaric oxygen.
Data in parentheses are percentages.
** One-sided Fisher's exact test.*
† Two-sided Pearson's chi-square test (two degrees of freedom).

COMMENT

Radiation-induced HC is an uncommon, but potentially devastating, side effect of pelvic radiotherapy. Of 1784 patients treated with radiotherapy for Stage Ib cervical cancer, the actuarial lifetime risk of major RTOG/EORTC grade 3 or worse urinary radiation morbidity has been reported at 1.0% at 5 years, 1.4% at 10 years, and 2.3% at 20 years.[10] Historically, severe HC was associated with a 44% mortality rate despite aggressive urinary diversion and cystectomy.[11]

Radiation-induced tissue ischemia alters tissue fibroblast function and collagen production, with resultant active fibrosis and reduced bladder compliance, as well as suboptimal capillary angiogenesis into hypoxic tissues. Wound repair in the bladder is impaired because of chronic scarring and may result in recurrent symptomatic hematuria.

For either RTOG/EORTC grade 1 or grade 2 late radiation-induced hematuria, the initial therapy should include urine cultures and cystoscopic and upper tract evaluation to exclude urinary tract infections, malignancy, and urolithiasis. Progression to RTOG/EORTC grade 3 or 4 macroscopic hematuria, with or without clots, typically requires inpatient medical or surgical intervention.[6,10] Traditional treatment methods include bladder irrigation, cauterization, oral or intravenous agents, intravesical chemical instillation, iliac artery embolization, urinary diversion, and cystectomy. However, no single treatment has resulted in satisfactory symptom control in most patients.[1]

HBO_2 therapy is an attractive management option for radiation-induced HC.[1,9] A recent review found that 145 (76%) of 190 reported patients demonstrated complete or partial symptomatic improvement, even among those who had failed multiple prior medical, cystoscopic, or intravesical therapies.[8]

HBO_2 therapy is the only form of treatment that promotes tissue healing and angiogenesis.[12] Delivery of HBO_2 within an enclosed pressurized chamber causes plasma oxygen hypersaturation and the creation of a steep oxygen gradient between capillaries and tissues. Dissolved oxygen in the plasma diffuses across capillary beds to improve local tissue oxygenation, increase collagen synthesis, and promote angiogenesis and tissue healing by neovascularization, with capillary in-growth into irradiated hypoxic tissues. Oxygen delivery can thereby be improved to tissues hypoxic because of prior radiation or mechanical or chemical injury.[13,14]

The risk factors for radiation-induced HC include a central axis radiation dose and extended radiation field.[10] The most common urologic cause of radiation-induced HC is pelvic radiotherapy for prostate cancer, as evidenced by 82% of patients in our series. The greater percentage of prostate cancer is a demographic reflection of patients referred to our hyperbaric facility.

Despite several prior failed therapies for bleeding episodes, 80% of our patients had either complete resolution or a partial reduction of symptoms after at least 12 months of follow-up. Even with a history of clot retention, 72% of patients showed clinical improvement.

Patients who were treated within 6 months of the onset of hematuria, independent of RTOG/EORTC grade or bleeding severity, experienced a significantly better response to HBO_2 treatment compared with patients who received HBO_2 therapy later than 6 months after the onset of hematuria. All 11 patients who had hematuria, with or without clot retention, had significant clinical improvement with early HBO_2 treatment. We postulate that early hyperbaric intervention is more effective at tissue regeneration and healing to break the vicious circle of chronic sloughing and resultant scarring in hypoxic irradiated bladder tissues.

In our series, the therapeutic response to HBO_2 therapy appeared to be age dependent, with a better outcome in younger patients. This finding, however, is inconclusive, because we were unable to account for all possible concomitant patient-related conditions in this retrospective review. Conditions that could possibly affect treatment outcome include diabetes mellitus, cigarette smoking, and atherosclerosis or vascular insufficiency.

We analyzed the effect of intravesical astringent instillation on the efficacy of subsequent HBO_2 treatment. No difference was found in the response rates among patients who received cauterization alone and those who received additional intravesical alum, silver nitrate, or formalin ($P = 0.552$). Even though these chemicals cause urothelial necrosis and cellular apoptosis, HBO_2 is apparently still able to promote tissue regeneration effects with resultant clinical improvement.

The modality and timing of pelvic radiotherapy did not affect the response rates significantly ($P = 0.950$). In more than 78% of patients, HBO_2 was useful for those who developed radiation-induced HC after primary, adjuvant, or salvage pelvic radiotherapy.

The total radiation dose data retrieved in 29 patients showed that those receiving higher radiation doses had a better therapeutic response. Of the 5 patients who had received more than 7000 cGy, 4 (80%) had complete or partial resolution of hematuria compared with 2 (67%) of the 3 who received less than 6000 cGy and 15 (71%) of the 21 who had received between 6001 and 7000 cGy. This comparison, however, was limited, because only 48% of all patients (29 of 60) had available dosimetry data and because these patients were treated with different radiation protocols using varying radiation field limits in different medical institutions for a variety of pelvic malignancies.

One of the limitations of this retrospective review was the lack of data on the frequency and severity of every hematuria episode that occurred both before and after HBO_2 therapy. It was also difficult to quantify how the hematuria episodes affected patients' quality of life because of a lack of clinically validated, disease-specific instruments to measure its impact. Furthermore, it was unclear whether the frequency of hematuria and the interval between consecutive hematuria episodes affected the therapeutic outcome.

Most published reports on radiation-induced HC treatment with HBO_2 have been retrospective case series, and, to our knowledge, no published randomized, prospective trials have been done. In a systematic review of the application of HBO_2 therapy for delayed radiation injuries, the investigators summarized and classified the levels of evidence for 17 reports on radiation cystitis.[8] All of them had American Heart Association level 5 evidence and National Cancer Institutes' Physicians Data Query level 3ii evidence, and 15 of the 17 papers were given the BMJ Publishing Group's designation of "likely to be beneficial" owing to the consistent and good results found in these case series. A well-designed randomized, prospective clinical trial that includes a validated, disease-specific quality-of-life assessment should be done to answer some of the limitations in our study.

CONCLUSIONS

In our study, delivery of HBO_2 therapy within 6 months of the onset of hematuria was associated with an increased therapeutic response rate, even in patients with a history of clot retention. The effectiveness of the treatment was independent of prior intravesical therapy and the timing of radiotherapy.

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