Hyperbaric Oxygen Therapy for Radiation Induced Proctopathy in Men Treated for Prostate Cancer

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Purpose: Radiation proctitis is a common complication following external beam radiation therapy and brachytherapy for prostate cancer. While 95% percent of radiation induced proctitis is temporary and self-limiting, up to 5% of patients experience toxicities that are refractory to conservative management. Hyperbaric oxygen has a well-defined role in treating chronic wounds, osteomyelitis, hemorrhagic cystitis and necrotizing fasciitis. We reviewed our experience with hyperbaric oxygen therapy for radiation induced proctitis in patients undergoing radiation treatment for prostate cancer.

Materials and Methods: From October 1998 to December 2003, 27 patients with radiation induced proctitis secondary to brachytherapy (4), external beam radiation therapy (16) or combined modality (7) for prostate cancer were treated with hyperbaric oxygen therapy at Virginia Mason Medical Center in Seattle, Washington. In all patients primary medical or endoscopic management had failed. Patients received 100% oxygen in a multiplace hyperbaric chamber at a pressure of 2.4 atmospheres absolute for 90 minutes 5 to 7 days weekly for an average of 36 sessions (range 29 to 60). Data were collected from a retrospective review of medical records following approval by the Institutional Review Board at Virginia Mason Medical Center.

Results: All 27 men completed the planned course of therapy. Of patients with bleeding 48% showed complete resolution after therapy, while 28% reported significantly fewer bleeding episodes. Of patients 50% noted complete resolution of fecal urgency. Six of the 8 patients (75%) with pain noticed some improvement after therapy, although no patients reported complete resolution of rectal pain. Of patients with rectal ulceration 21% showed complete resolution of the ulcer on posttreatment endoscopy, while 29% showed evidence of improvement. Six patients (43%) had no change or worsening of rectal ulcers. Overall 67% of patients had a partial to good response, while 33% showed no response or disease progression.

Conclusions: This series of patients showed a good overall response rate to hyperbaric oxygen for radiation induced proctopathy after other attempts at management had failed. Hyperbaric oxygen is generally well tolerated and it remains an important treatment option for managing this common and difficult disease.

Key Words: rectum, radiation therapy, prostatic neoplasms, complications, proctitis

Radiation proctitis is a common complication following XRT and brachytherapy for prostate cancer. This typically presents with rectal pain, urgency, diarrhea, frequency or bleeding. Radiation induced toxicities are graded on a scale of 1 to 5 according to criteria established by RTOG and they can present acutely or in delayed fashion several months after treatment (table 1).[1] Of radiation induced proctitis 95% is RTOG grade 1 or 2, temporary and self-limiting. However, up to 5% of patients experience grade 3 to 5 toxicities that are refractory to conservative management and require more aggressive therapy.[1] Grade 3 to 5 radiation induced proctitis represents a particular therapeutic challenge and it greatly impacts patient quality of life with considerable life threatening morbidity.

Traditional treatment options described for radiation induced proctitis are various oral medications and rectal suppositories, including steroids, sulfasalazine, aspirin products, oral and rectal sucralfate, and formalin.[2] More recently direct endoscopic coagulation of visible lesions with an argon beam plasma laser has shown promising results.[3] HBO_2 has a well-defined role in treating chronic wounds, osteomyelitis, hemorrhagic cystitis and necrotizing fasciitis, and recently it has emerged as a treatment option for radiation induced proctitis refractory to other attempts at management.[4] By increasing oxygen partial pressure in affected tissues, HBO_2 delivery promotes angiogenesis and, thus, nutrient influx and ultimately the repair of damaged, poorly vascularized tissue.[4,5] We reviewed our experience with HBO_2 for severe, medically refractory radiation induced proctitis experienced by patients treated with radiotherapy for prostate cancer.

METHODS

From October 1998 to December 2003, 27 patients with radiation induced proctitis secondary to brachytherapy (4), XRT (16) or combined XRT and brachytherapy (7) for prostate cancer were treated with hyperbaric oxygen therapy at Virginia Mason Medical Center in Seattle, Washington. All patients had RTOG acute grade 3 or 4, or chronic grade 2 to

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TABLE 1. *RTOG radiation induced toxicity scales*

RTOG Grade	Acute (less than 90 days)	Chronic (greater than 90 days)
1	2–3 Stools/day, rectal discomfort not requiring medication	Up to 5 stools/day, some rectal mucus or bleeding
2	4–6 Stools/day, nocturnal stools, moderate cramping, diarrhea + pain requiring medications	Greater than 5 stools/day, moderate diarrhea, excessive rectal mucus or intermittent bleeding
3	7–9 Stools/day, incontinence, severe cramping, diarrhea + pain requiring medications	Rectal obstruction or bleeding requiring surgical interventions
4	Obstruction, perforation, fistulization, bleeding requiring transfusion, pain requiring surgical decompression or diversion	Rectal necrosis, perforation, fistulization
5	Death	Death

4 toxicities and in all primary medical or endoscopic management had failed (table 1). Most patients were referred from elsewhere for further management of symptoms and complete data regarding dose and fields of delivered radiation were unavailable. All patients had endoscopically confirmed injuries to the rectum. One patient was also noted to have transverse colon and stomach involvement. Patients received 100% oxygen in a multiplace hyperbaric chamber at a pressure of 2.4 atmospheres absolute for 90 minutes 5 to 7 days weekly for an average of 36 sessions (range 29 to 60). Data were collected from a retrospective review of the medical records after approval by the Institutional Review Board at Virginia Mason Medical Center.

Responses to therapy were graded as good, partial or failed based on the change in symptoms, amount of rectal bleeding, need for further management and post-HBO_2 endoscopic evaluation of treatment response. Responses to HBO_2 were considered good if patients had complete resolution of rectal bleeding, absence of ulcers on followup endoscopy and return to premorbid bowel function. Partial responders demonstrated at least 50% improvement in bleeding episodes, evidence of rectal ulcer healing on endoscopy and at least 50% improvement in symptoms. Patients in whom HBO_2 failed demonstrated worsening symptoms with disease progression.

RESULTS

Patient Characteristics

Mean patient age was 71 years (range 53 to 81). Median time between the completion of radiation or brachytherapy and beginning HBO_2 treatment was 19 months (range 3 to 240). Mean patient followup after HBO_2 treatment was 13 months (range 1 to 60). Patients received a median of 68 Gy for XRT alone and 144 Gy for brachytherapy. Patients treated with combined modality therapy received a mean of 40 to 50 Gy with XRT combined with 90 to 100 Gy by brachytherapy.

TABLE 2. *Treatments before HBO_2*

Prior Treatment	No. Pts
Oral medication (5-aminosalicylic acid, sulfasalazine, Feldene®)	2
Rectal medication (Proctofoam®, mesalamine, Proctocort®, sucralfate enema, formalin)	20
Laser coagulation	3
Argon plasma coagulation	2
Diverting colostomy	2

TABLE 3. *Patient characteristics*

No. pts	27	
Mean age (range)	71.8	(53–82)
No. bleeding via rectum (%)	25	(93)
No. pts requiring blood transfusions before HBO_2 (%)	6	(22)
No. pain (%)	8	(30)
No. fecal urgency (%)	4	(15)
No. rectal ulceration on endoscopy (%)	14	(52)
Median mos symptom duration before HBO_2 (range)	8	(1–132)
Mean mos XRT completion–beginning HBO_2 (range)	19	(3–240)
Mean no. HBO_2 treatments (range)	36	(29–60)

HBO_2 Treatment and Complications

All 27 men completed the planned course of hyperbaric therapy. Before HBO_2 patients received various therapies for symptoms related to radiation induced proctopathy (table 2). A total of 20 patients tried rectal medications before HBO_2. Fewer patients had received oral medications (2), laser coagulation (3) or argon plasma treatment (2). Two patients underwent diverting colostomy secondary to profound symptoms. Table 3 lists patient characteristics before HBO_2. Followup data were available on all patients. Treatment was complicated by the need for pressure equalizing tympanostomy tube placement in 3 patients, transient oxygen induced myopia in 2 and a hyperbaric oxygen induced seizure in 1. All patients underwent endoscopic evaluation of the distal colon/rectum before HBO_2 therapy and 25 of 27 underwent posttreatment endoscopy.

Patient Outcomes

Table 4 lists patient outcomes. Of patients with bleeding 48% showed complete resolution after therapy, while 28% reported significantly fewer bleeding episodes. Two of 4 of patients with fecal urgency noted complete resolution, while 1 described some improvement. Six of the 8 patients with

TABLE 4. *Patient outcomes*

Response	No. Pts (%)
Bleeding:	25
Resolved	12 (48)
Improved	7 (28)
Unchanged	5 (20)
No data	1 (4)
Fecal urgency:	4
Resolved	2
Improved	1
Unchanged	0
No data	1
Pain:	8
Resolved	0
Improved	6
Unchanged	1
No data	1
Rectal ulcer:	14
Resolved	2
Improved	5
Unchanged	6
No data	1
Overall response:	27
Good	10 (37)
Partial	8 (30)
No change	9 (33)

pain noticed some improvement after therapy, although no patients reported complete resolution of rectal pain. Two of 14 patients with rectal ulceration showed complete resolution of the ulcer on posttreatment endoscopy, while 5 showed evidence of improvement. Six patients had no change or worsening of rectal ulcers.

Of patients 67% had a partial to good response overall, while 33% showed no response or progression of the condition. Six of the 9 patients in whom HBO_2 therapy failed had worsening of preexisting ulcers, while 1 had severe ulceration during therapy. Two patients had failure with worsening symptoms or persistent rectal bleeding. Seven of the 9 patients showing no response to therapy, ultimately required diverting colostomy to manage symptoms.

DISCUSSION

Radiation proctopathy is seen after radiotherapy for any pelvic malignancy, including that of the bladder and prostate. Due to the relatively fixed position of the rectum to the prostate the rectum is commonly affected by XRT and brachytherapy administered for prostate cancer. In a recent study Peeters et al reported RTOG acute grade 3 and chronic grade 2 or greater gastrointestinal toxicity in 5% and 25% of men, respectively, undergoing XRT for prostate cancer.[6]

Although the complex pathological processes of radiation induced injury to the rectum begins immediately following exposure, it may require weeks to months to become clinically apparent.[7,8] It is estimated that up to 30% of patients undergoing pelvic radiotherapy have acute rectal toxicities with 15% of patients experiencing chronic symptoms.[8] Symptoms of acute rectal toxicity typically occur within 6 weeks of radiotherapy, while chronic injuries become clinically evident 9 months to 2 years following treatment.[8] Acute radiation injury is characterized histologically by the death of rapidly proliferating cells and destruction of the normal cellular tissue components.[7] Symptoms of pain, diarrhea and mucous production arise from loss of the epithelial cell layer in the rectum.[7] Late effects of radiation are seen from damage to slowly replicating cells, and by the induction of proinflammatory and pro-coagulation cytokine signaling pathways, leading to edema, fibrosis and ultimately ischemia in the muscularis.[7]

There are no standard therapies for radiation induced proctopathy and a number of treatments have been described with varying efficacy, including pharmacotherapy, sclerotherapy and HBO_2. By increasing systemic oxygen partial pressure HBO_2 increases the delivery of oxygen to ischemic tissues, thereby promoting angiogenesis, nutrient influx and fibroblast proliferation.[5] Several small retrospective series suggest that hyperbaric oxygen can successfully treat radiation induced proctopathy with response rates between 40% and 60%.[9–11] A recent randomized, placebo controlled trial showed statistically significant improvement in wound healing with hyperbaric oxygen in patients with late radiation tissue necrosis compared with patients receiving normal air at 1 atmosphere.[12]

The most common complications experienced with HBO_2 delivery are mild and transient, including otic barotrauma, confinement anxiety and temporary myopia. More severe effects include rare seizures from central nervous system oxygen toxicity and pulmonary oxygen toxicity.[4,13] The reported incidence of seizures during routine HBO_2 therapy at 2.36 atmospheres absolute pressure is 1/3,300 treatments with up to 20% of patients experiencing reversible myopia.[5,14] In a series of 782 patients undergoing HBO_2, 17% experienced ear pain with 3.4% having visually confirmed otic barotrauma.[13] In our series of 27 men HBO_2 was tolerated extremely well with 1 severe side effect reported, that is a seizure without sequelae. Of patients 7% experienced mild myopia during treatment.

Our study population consisted of men with severe radiation proctopathy after radiotherapy for prostate cancer in whom multiple attempts at management had failed, including steroid injection, anti-inflammatory suppositories and argon plasma laser coagulation. Overall 66% of patients in our study showed a partial to complete response to HBO_2 therapy. Due to our relatively small sample size no inferences can be made on outcomes in relation to prior treatments received. Patient outcomes varied by specific symptom and radiation induced injury. Patients with rectal bleeding and urgency responded well to HBO_2 with almost 50% showing a complete response with no further bleeding episodes. Although 6 of 8 patients with rectal pain reported improved symptoms after HBO_2, no patients reported complete resolution of pain. Rectal ulcers showed favorable responses to HBO_2 with 7 of 14 patients in our series showing a partial or complete response. Most patients who ultimately failed to respond to HBO_2 in our series had progressive rectal ulceration, requiring diverting colostomy.

We acknowledge several limitations to our study. We were unable to standardize pretreatment symptoms and did not characterize patients using a standard scoring system, such as the Late Effects of Normal Tissues-Subjective-Objective Management Analytic scales for measuring the effects of radiotherapy.[15] We used a more subjective approach to grading overall responses to therapy, which makes it difficult to directly compare our outcomes to those in other series. However, our series shows a favorable response (67% improved) with HBO_2 in men with severe, treatment refractory radiation proctitis. Fewer than 20% of patients with this degree of injury heal spontaneously. Although this study is a retrospective, nonrandomized review, our results suggest that a significant response is achievable with HBO_2 in a challenging patient population.

It is not unusual for radiation induced proctopathy to present with associated voiding symptoms. We have previously reported the efficacy of HBO_2 for radiation induced hemorrhagic cystitis.[16] Of patients in that series 80% showed partial to complete resolution of hematuria after HBO_2 with the greatest response observed in those treated within 6 months of the onset of hematuria.[16] The response to HBO_2 also depended on the severity of presenting hematuria.

Although HBO_2 is an effective modality for radiation induced proctopathy, our outcomes are less pronounced than those of HBO_2 for radiation induced hemorrhagic cystitis. Studies in patients with hemorrhagic cystitis have shown that 40 hyperbaric treatments is the optimal number for a durable symptom response.[17] To our knowledge the ideal number of treatments in men with radiation proctopathy remains unknown.

Abbreviations and Acronyms

HBO_2	=	hyperbaric oxygen therapy
RTOG	=	Radiation Therapy Oncology Group
XRT	=	external beam radiation therapy

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