

Rate of delivery of hyperbaric oxygen treatments does not affect response in soft tissue radionecrosis.

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Hampson NB, Corman JM. Rate of delivery of hyperbaric oxygen treatments does not affect response in soft tissue radionecrosis. *Undersea Hyperb Med* 2007; 34(5):000-000. Background: Soft tissue radiation necrosis (STRN) is effectively treated with hyperbaric oxygen (HBO₂), believed to result from stimulation of angiogenesis in radiation-injured tissue. Thirty to forty HBO₂ treatments are usually recommended for STRN. For various reasons, different hyperbaric facilities offer these treatments once or twice daily and from 5-7 days weekly. It is not known whether the clinical response differs as a result of the rate of administration of HBO₂ treatments. Methods: Details of hyperbaric treatment courses of patients treated for radiation enteritis/proctitis (n=65) and cystitis (n=94) at a single institution were reviewed. Outcomes were compared with the total number of HBO₂ treatments administered and also rate of treatment administration. Results: Responses were similar for both forms of STRN whether the patient averaged fewer or greater than 5 treatments per week, or even ≤ 3 versus ≥ 7 treatments weekly. Outcome did differ, however, dependant on the total number of treatments administered. Response was better in patients receiving 30 or more total treatments, as compared with fewer. Conclusions: Soft tissue radionecrosis of the gastrointestinal tract or bladder is (1) effectively treated with hyperbaric oxygen, (2) has a higher response rate if at least 30 treatments are administered, and (3) is equally responsive to rates of hyperbaric treatment ranging from 3 or fewer to 7 or more treatments per week.

INTRODUCTION

Hyperbaric oxygen (HBO₂) therapy is effective treatment for many forms of chronic radiation tissue injury. Both soft tissue radiation necrosis (STRN) and osteoradionecrosis are indications accepted by the Undersea and Hyperbaric Medical Society for hyperbaric oxygen treatment (1). In a recent evidence-based review by Feldmeier and Hampson, STRN at numerous sites in the body was found to be effectively managed with HBO₂ treatment (2).

The pathophysiology of chronic radiation tissue injury involves fibrosis and endarteritis leading to loss of capillary density and resultant tissue hypoxia (3). HBO₂ is felt to be effective

in STRN by enhancing angiogenesis and, in so doing, providing oxygen to meet the metabolic demands of radiation injured tissues. Marx has shown a dose dependent increase in vascular density in irradiated animals treated with hyperbaric oxygen (4). The exact mechanism by which this occurs is not completely understood but is under investigation.

Clinically, STRN is treated with HBO₂ using protocols that range in maximum pressure from 2.0 to 2.5 atmospheres absolute (atm abs) and in oxygen breathing time from 90 to 120 minutes (1). Patients typically receive 30 to 40 treatments, delivered 5, 6 or 7 days weekly and once or twice daily, depending upon the staffing and physical capacity of the hyperbaric treatment facility involved.

No studies exist to determine whether the rate of delivery of hyperbaric treatments influences outcome in chronic radiation tissue injury. While treatment approaches differ between facilities, it remains unknown whether administration of varying numbers of treatments per day or per week is equivalent therapy. This study was performed to analyze outcomes in two forms of STRN, radiation enteritis/proctitis and hemorrhagic radiation cystitis, with regard to rate of administration of HBO₂ therapy.

METHODS

We have previously reported outcomes in patients treated with HBO₂ at Virginia Mason Medical Center (VMMC) in Seattle, for STRN of the gastrointestinal tract and bladder (5,6,7). With regard to radiation-induced enteritis/proctitis, 65 consecutive patients ranging in age from 36-84 years (median 65 years) and treated with HBO₂ from 1991-2003 were reviewed and reported. They are the population used for analysis of response of STRN of the bowel to varying rates of HBO₂ administration in the present study. To briefly summarize that experience, patients received from 22-60 HBO₂ treatments (median 30 treatments). Outcomes were retrospectively graded by an independent records reviewer not associated with administration of the hyperbaric treatment and categorized as (1) complete response (greater than 90% reduction in symptom frequency or subjective symptom complaints and endoscopic documentation of healing when available), (2) partial response (50-90% reduction in symptom frequency or subjective measure of improvement and endoscopic documentation of improvement), or (3) failure (less than 50% measurable or subjective improvement, minimal or no endoscopic improvement or the need for surgical intervention). Outcomes from hyperbaric treatment are shown in Table 1.

Response Category	Radiation Enteritis/Proctitis (n=65)	Radiation Cystitis (n=94)
Complete	43% (n=28)	40% (n=38)
Partial	25% (n=16)	43% (n=40)
Failure	32% (n=21)	17% (n=16)

Table 1. Outcomes of patients with radiation-induced enteritis/proctitis and radiation cystitis treated with hyperbaric oxygen.

In 2003, outcomes in 62 consecutive patients with hemorrhagic radiation cystitis treated with HBO₂ at VMMC from 1988-2001 were reported. As above, retrospective review was performed by an independent reviewer and patient outcomes categorized as (1) complete (resolution of hematuria), (2) partial (marked improvement in hematuria), or (3) failure (unchanged or worsened hematuria) following HBO₂ treatment. Since that time, 32 additional patients were treated through 2006 and are combined with the previous group for the present analysis. The study population with STRN of the bladder thus includes 94 consecutive patients ranging in age from 15-91 years (median 74 years) and receiving from 4-60 HBO₂ treatments (median 30 treatments). Outcomes following hyperbaric treatment are also shown in Table 1. See the respective publications for the full details of methods and results of these initial studies (5,6,7).

At VMMC, patients with STRN are offered once or twice daily hyperbaric treatment from Monday through Friday and once daily on Saturday and Sunday, scheduled at their discretion. Within this construct, they attend treatment from 0-12 times weekly, depending on their own circumstances. For the present analysis, treatment records were reviewed to determine the date of each patient's first and last hyperbaric treatments. The total number of days encompassed in the course were counted, divided into total number of treatments that the patient received to obtain an average treatment per day rate. Average treatment per week (per 7 days) rate was then calculated from this.

To determine whether rate of treatment was associated with outcome, number of responders (partial plus complete, as defined above) vs. nonresponders (failure) for each of the two sites and then both sites combined were compared with regard to those receiving an average of 5 or fewer treatments per week and more than 5 treatments per week (2 x 2 contingency table, Fisher’s Exact Test). The same analysis was then repeated with regard to those receiving an average of 3 or fewer treatments per week with those who received 7 or more treatments per week. Finally, outcome with regard to total number of treatments received independent of rate was analyzed by comparing responders vs. nonresponders among those who received fewer than 30 treatments with those who received 30 or more total treatments.

RESULTS

Hyperbaric treatment courses for patients treated for radiation enteritis/proctitis ranged from 9-333 days (median 43 days). Individual patients averaged from 1-13 treatments per week over their course of therapy (median 5 treatments per week).

Treatment courses for those with radiation cystitis ranged from 4-101 days (median 44 days) and averaged from 2-12 treatments per week (median 5 treatments per week). Patients treated more than 5 times weekly typically were from out of town and staying with friends, relatives or at a hotel. They tended to be more interested in accelerated therapy. Patients with prolonged treatment courses either had other medical issues which needed to be addressed during their course of hyperbaric therapy or were poorly compliant with attendance for personal reasons.

Among patients treated for radiation enteritis/proctitis, radiation cystitis, or both combined, there were no significant differences between those averaging 5 or fewer treatments per week compared with those averaging over 5 treatments per week (Table 2a; p = 0.4339, 0.2794, and 1.0000, respectively). There were also no significant differences in outcome for the same groups between those averaging 3 or fewer treatments per week when compared with those averaging 7 or more treatments per week (Table 2b; p = 1.0000, 1.0000, and 1.0000, respectively).

When comparing those who received

Table 2-a

	Radiation Enteritis/Proctitis		Radiation Cystitis		Combined	
	≤ 5 HBO ₂ weekly	> 5 HBO ₂ weekly	≤ 5 HBO ₂ weekly	> 5 HBO ₂ weekly	≤ 5 HBO ₂ weekly	> 5 HBO ₂ weekly
Responders	20 (62%)	24 (73%)	37 (88%)	41 (79%)	57 (77%)	65 (76%)
Nonresponders	12	9	5	11	17	20
	P = 0.4339 (NS)		p = 0.2794 (NS)		p = 1.0000 (NS)	

Table 2-b

	Radiation Enteritis/Proctitis		Radiation Cystitis		Combined	
	≤ 3 HBO ₂ weekly	≥ 7 HBO ₂ weekly	≤ 3 HBO ₂ weekly	≥ 7 HBO ₂ weekly	≤ 3 HBO ₂ weekly	≥ 7 HBO ₂ weekly
Responders	8 (67%)	10 (67%)	2 (67%)	11 (65%)	10 (67%)	21 (66%)
Nonresponders	4	5	1	6	5	11
	p = 1.0000 (NS)		p = 1.0000 (NS)		p = 1.0000 (NS)	

Table 2. Contingency tables for patients treated for radiation enteritis/proctitis, radiation cystitis, or both conditions combined, comparing (a) those who averaged 5 or fewer HBO₂ treatments per week with those averaging greater than 5 treatments per week, and (b) those who averaged 3 or fewer HBO₂ treatments per week with those averaging 7 or more treatments per week (Fisher’s Exact Test).

	Radiation Enteritis/Proctitis		Radiation Cystitis		Combined	
	< 30 Total HBO ₂	≥ 30 Total HBO ₂	< 30 Total HBO ₂	≥ 30 Total HBO ₂	< 30 Total HBO ₂	≥ 30 Total HBO ₂
Responders	0 (0%)	44 (71%)	14 (67%)	64 (88%)	14 (58%)	108 (80%)
Nonresponders	3	18	7	9	10	27
	p = 0.0304*		p = 0.0432*		p = 0.0334*	

Table 3. Contingency tables for patients treated for radiation enteritis/proctitis, radiation cystitis, or both conditions combined, comparing those who fewer than 30 total HBO₂ treatments with those who received 30 or more total treatments (Fisher’s Exact Test).

fewer than 30 total hyperbaric treatments with those who received 30 or more total treatments, the response rate was significantly greater in the latter group for patients treated for radiation enteritis/proctitis, radiation cystitis, or both conditions combined ((Table 3; p = 0.0304, 0.0432, and 0.0334, respectively). The number of responding and nonresponding patients with varying numbers of total HBO₂ treatments is shown in Figure 1.

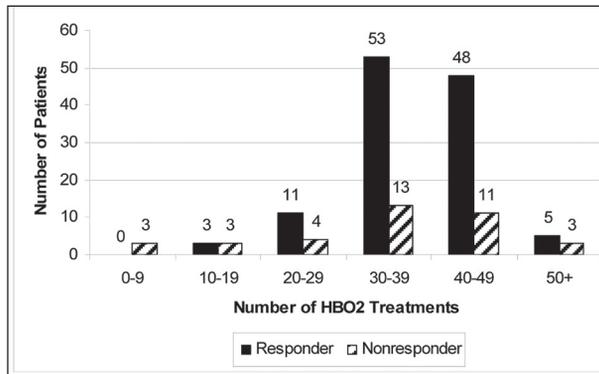


Fig. 1. Number of responders and nonresponders to various numbers of HBO₂ treatments.

DISCUSSION

Over one million new cases of invasive cancer are diagnosed annually in the United States and approximately one-half of those patients receive radiation therapy as part of the management of their malignancy (8). While long-term complications occur in fewer than 5% of

patients and are therefore relatively rare (3), the number of patients treated yields the potential for many cases of chronic radiation tissue injury or necrosis.

As noted, HBO₂ has been shown to be effective treatment for many types of chronic radiation injury. In their evidence-based review, Feldmeier and Hampson combined the results of published series and found hyperbaric treatment response rates of 96% for radiation enteritis/proctitis (36 resolved, 60% improved) and 76% for radiation cystitis (2). When the enteritis/proctitis evidence was graded by the American Heart Association scheme, the results were felt to support an AHA IIb indication category (“fair to good evidence provides support”). The results of radiation cystitis series were so consistent that a Class IIa AHA designation was assigned (“acceptable and useful”). Further, hyperbaric treatment for soft tissue radionecrosis is covered by Medicare and most third-party payors.

HBO₂ is widely used for treatment of STRN both in the US and internationally. While treatment pressures and oxygen breathing times do vary, they are relatively similar from facility to facility. A bigger difference, and one with more impact on patient access to care, is the rate that treatments are administered. From a facility standpoint, availability of once vs. twice daily treatment is often controlled by chamber capacity issues. The number of days that a facility provides non-emergent treatment weekly is usually governed by staffing and budgetary issues.

From a patient standpoint, many desire to complete their prescribed course of treatment as rapidly as possible. This is particularly true for patients who live a long distance from the hyperbaric facility. If they commute daily, many prefer to complete two treatments per day, if possible. If they live too far to commute and must pay for local housing, most are anxious to expedite therapy, minimize costs for housing, and return home to their families and jobs as soon as possible.

Until now, there have been no published data to guide the decision of rate of therapy. Although the mechanism of HBO₂-induced angiogenesis in irradiated tissue is not completely understood, there is presumably some stimulus produced by the hyperbaric exposure, followed by period of metabolic response. No animal studies have examined whether equivalent angiogenesis is produced by once and twice daily treatment. In clinical discussions of once vs. twice daily treatment, the question is usually raised as to whether there is sufficient time for the metabolic response necessary for angiogenesis to occur if the treatments are administered twice daily.

The present study demonstrates that the rate of hyperbaric treatment does not influence the therapeutic outcome for two forms of STRN. Forty HBO₂ treatments delivered in 20 days should be expected to induce the same therapeutic response as 40 treatments delivered in 60 days. It is also demonstrated that response is not simply a function of days of treatment. Twenty treatments in 20 days would not be expected to yield the same outcome as 40 treatments in 20 days. Patient response for both conditions correlated significantly with total number of treatments. Patients who received fewer than 30 treatments had a poorer response rate than those receiving 30 or more.

The implications for clinical practice are many. First, a patient being treated for radiation enteritis/proctitis or cystitis should not be denied twice daily treatment out of concern for poorer

outcome. If facility capacity with regard to chamber availability and staffing are adequate, twice daily treatment can be offered to those who desire it. Secondly, there does not appear to be a reason for concern if a patient prolongs treatment over a long period. Those who received 3 treatments or fewer per week did as well as those who completed 5, 7 or more weekly. As such, a patient's treatment should not be discontinued solely for the issue of infrequent attendance. Finally, from a facility standpoint, flexing patient treatment schedules from once to twice daily as capacity allows is an excellent method for leveling production and reducing costs by minimizing variation as represented by peaks and troughs in patient volume.

In this analysis, total numbers of treatments fewer or greater than 30 were compared for efficacy because that was the median number administered. At the time patients were treated early in each series, 30 treatments were typically prescribed. It should be noted that 40 treatments is the number generally recommended now for soft tissue radionecrosis (1). In radiation cystitis for example, 40 hyperbaric treatments is the optimal number for both acute resolution of symptoms and a long-term durable result (9). Shorter treatment courses are associated with a higher incidence of relapse.

The potential limitation to this study is the fact that the patients self-selected their own treatment rates and were not randomized to higher versus lower rates. Such a randomized trial would be quite difficult to accomplish. In our experience, even when patients are scheduled for once or twice daily treatment, they rarely complete their entire course of therapy exactly on schedule. In fact, as evidenced by the present data, the study performed is more "real world" than would be either arm of a randomized trial. Further, bias from self-selection should only be a concern if a difference had been demonstrated associated with treatment rate.

To summarize, soft tissue radionecrosis of

the gastrointestinal tract or bladder is (1) effectively treated with hyperbaric oxygen, (2) has a better response rate to therapy if at least 30 treatments are administered, and (3) is equally responsive to rates of hyperbaric treatment ranging from 3 or fewer to 7 or more treatments per week.

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