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HYPERBARIC OXYGEN THERAPY FOR RADIATION-INDUCED HAEMORRHAGIC CYSTITIS

Andrew Waring and Harry Oxer

Key words

Hyperbaric oxygen, irradiation, treatment.

Summary

A retrospective study of the ten year experience of the Fremantle Hospital Hyperbaric Unit in the treatment of radiation-induced haemorrhagic cystitis. This is the largest reported series in Australia and the second largest found in the literature. The objective of this study is to examine the benefit of a course of hyperbaric oxygen therapy in this condition, for which other treatment modalities are often inadequate, temporary and associated with much morbidity. A majority of patients obtained at least symptomatic benefit with minimal discomfort and no major complications. There was a marked decrease in the requirement for blood transfusion. This suggests that hyperbaric oxygen (HBO_2) therapy in radiation-induced haemorrhagic cystitis is both efficacious and well-tolerated, and should be considered for all patients with this condition. Further trials, with more objective outcome measurements, need to be undertaken.

Introduction

Irradiation is a common therapy for a variety of malignant tumours in the pelvic region. Haemorrhagic radiation-induced cystitis and proctitis are side effects that

occur in up to 10% of patients.[1,2] The consequences of these can be life-threatening and the symptoms debilitating.[3] Multiple blood transfusions are often required.

Conventional treatment modalities by urologic surgeons for haemorrhagic cystitis include fulguration,[3] instillation of formalin,[3,4] silver nitrate,[5] alum,[6] sodium pentosulfanpolysulphate,[2] hydrostatic bladder dilatation, and hypogastric artery ligation.[6] All of these have disappointing results in symptomatic relief. Furthermore, while sometimes ameliorating symptoms, they do not address the long-term healing of the underlying radiation damage.[7] Failure of these other conservative modalities may lead to a requirement for urinary diversionary surgery, with or without cystectomy, and further stresses on already debilitated patients.

Hyperbaric oxygen (HBO_2) therapy simultaneously addresses both these symptomatic and healing issues. Previous studies have suggested that hyperbaric oxygen treatment in this condition is beneficial, has minimal morbidity and is well tolerated.[1,2,7-9] This study examines the experience and results of the Fremantle Hospital Unit in the past ten years.

Methods

Between December 1989 and February 1998, 26 patients (male 21, female 4, average age 69 years (40-82) underwent 30 courses of hyperbaric oxygen at Fremantle Hospital for a total of 676 treatments. The average number of treatments was 22 (range 14-50). One patient was excluded from the analysis unable to continue beyond the first treatment.

The Fremantle Hospital Hyperbaric unit has a multi-place chamber. Patients are seated in armchairs in the chamber during treatment and 100% oxygen is delivered via a head hood. All patients are treated with the "FH10" treatment table (105 minutes total, at a pressure of 2 ATA), for 6 days per week. The usual number of treatments was twenty-four (four weeks), with a medical assessment and option to continue for a further 2-3 weeks at this time. Patients were followed up one month later by telephone, and if required, by personal interview. Patient data was collected from hospital, unit and consultant records, and studied retrospectively.

Results

Patients were referred to the Fremantle Hospital Hyperbaric Unit for treatment of their haemorrhagic radiation-induced cystitis on an average of 34 (range 1-96) months after radiotherapy (average dose 63 Gy). Three patients were referred by their radiation oncologist, and 22 by their urologist. The principal underlying diagnoses were carcinoma of the prostate and bladder. Eleven of the patients had undergone previous forms of symptomatic treatment, such as alum irrigation and fulguration of the bladder. Fifteen patients had required blood transfusion, with an average need for 6 units (range 2-17). All had radiation damage and cystitis, that was cystoscopically proven in 23 (not recorded for 1 and the other had necrosis of the bulbar urethra). Symptomatically, the cystitis was described as severe in nine and moderate in sixteen.

Immediately following their course of hyperbaric therapy, patients were assessed symptomatically by the unit director (HFO). Twenty-four patients (96%) reported symptomatic improvement. Six had complete resolution of haematuria and eleven reported a marked reduction. Decreased intermittent haematuria persisted in 1 patient, there was no change in 4 and information was not recorded for 2 patients. Other symptomatic improvements included a decrease in nocturia, frequency and strangury. There was no correlation between improvement and age, sex, or the original diagnosis.

Follow-up cystoscopy was available for 17 patients. Two were reported as normal cystoscopy, "improvement" (not otherwise specified) in a further 2, recurrent tumour was present in 2, ongoing radiation cystitis in 5. The remaining six cystoscopies had a range of results (infection, erythema, old clots).

At initial follow-up (usually one month later) each patient was assessed symptomatically by the unit director. Ten described complete, twelve partial and the remaining three poor or no response to the therapy. No patient died during the course of treatment, however two died within 3 months of completion from causes unrelated to the treatment (both due to their underlying conditions). Mean follow-up time was 5 months (range 1-18 months).

Complications in the series were minimal and none related specifically to the hyperbaric treatment. Two patients had severe persistent haematuria (one related to the underlying malignancy) during the course of treatment that required admission to hospital.

Five patients required further courses of hyperbaric treatment for recurrent haematuria. All these patients had had at least 18, and an average of 22, initial treatments. Four had repeat cystoscopies between the treatment courses; two showed continuing but diminished radiation damage, one had evidence of infection and point bleeding and one had recurrent tumour. The remaining patient was re-treated on symptoms alone.

Discussion

The underlying pathophysiology of haemorrhagic radiation-induced cystitis involves a

combination of mucosal oedema, vascular telangiectasis, obliterative endarteritis[3] and smooth muscle fibrosis.[1,2,8,10] Endarteritis leads to ischaemia and hypoxia of the mucosa, with the clinical end-result of ulceration and bleeding.[1,8] Hyperbaric oxygen repairs these abnormalities by creating an angiogenic oxygen gradient, acting via tissue macrophages.

At 2 ATA using 100% oxygen, the tissue oxygen tension is increased 10 fold compared with ambient air and alternating HBO_2 treatments with the relative hypoxia encountered in room air, ensures the necessary oxygen gradients, and stimulus required.[6,9] This leads to new vessel formation, increasing the vascular density 8 to 9 fold,[8] ensuring a much improved oxygen supply to the hypoxic tissue.[3,10]

Although this angiogenic effect is due to hyperoxia[1] the same effect is not obtained breathing 100% normobaric oxygen as the driving gradient is insufficient to trigger the process. Follow-up at 4 years suggests these changes are permanent.[8]

Additionally, induction of hyperoxia improves wound healing and immune function (microbial killing is enhanced by augmentation of the "oxidative burst" phase

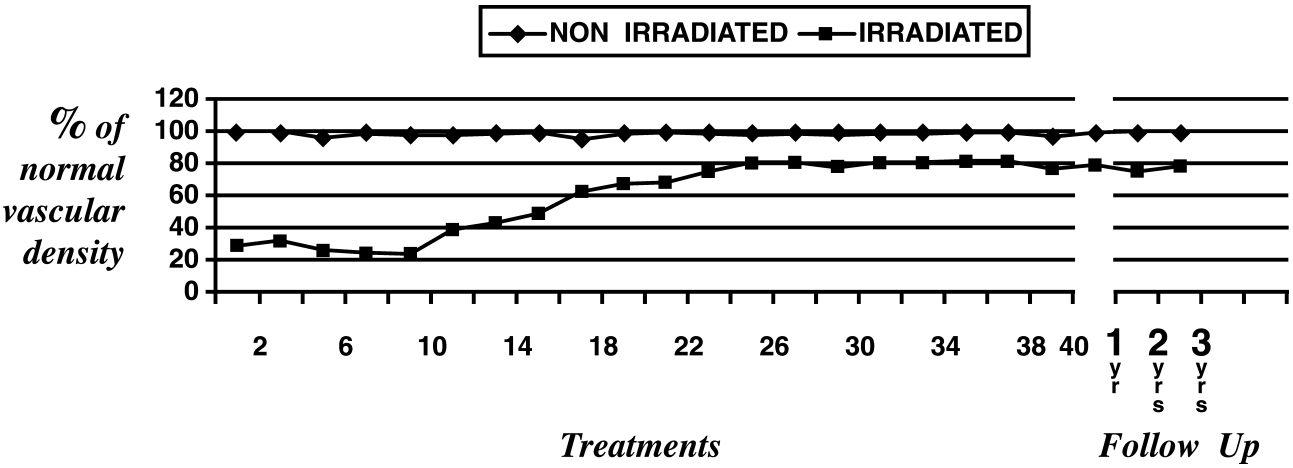

Figure 1. The effect of hyperbaric oxygen on radiation-damaged tissue.

TABLE 1

RESULTS OF OTHER STUDIES

Investigator	Patients	Pressure (ATA)	Duration (Minutes)	Times treated	Outcome	Notes
Norkool et al.[8]	14	2.4	90	28 (9-58)	8/14 complete resolution. 2/14 marked improvement. 3/14 little improvement.	Later shown to have malignancy recurrence
Weiss et al.[1]	13	2.0	120	60	12/13 durable cessation of haematuria	
Bevers et al.[7]	40	3.0	90	20	37/40 complete cessation or improvement.	Recurrence 0.12/year
Lee et al.[12]	20	2.5	100	44	16/20 haematuria resolved. 2/20 markedly decreased.	All female patients
Weiss et al.[6]	3	2	120	60	3/3 good response	
Schoenrock et al.[3]	1	2	105	19	All healed.	
TOTALS	**91**	**Av 2.6**	**Av 100**	**Av 33**	**81/91 At least "markedly improved"**	

of phagocytosis) in the setting of ischaemia.[1,3] Figure 1, adapted from Marx,[11] demonstrates the increase in vascularity over time in irradiated tissue exposed to hyperbaric oxygen. After an initial lag phase, the relative vascular density increases from approximately 30% to 80%, an effect that is sustained well beyond the period of treatment. Previous experience suggests that at least 20 treatments are necessary to achieve optimal benefit in both angiogenesis and immune function, following which there is a plateau in vascular density, which is maintained well beyond the duration of treatment.[11]

Results from this study confirm the findings of previous studies (Table 1) that the overwhelming number of patients respond well to hyperbaric treatment with a minimum of complications or side effects. Other treatment options at this time are of limited value and often are associated with significant morbidity. Additionally, many of the patients were considered refractory to conventional methods of treatment.

Patients receive hyperbaric treatment for radiation-induced haemorrhagic cystitis on the basis of symptoms. In this study, 96% of patients reported symptomatic improvement; a lesser number had complete resolution of their haematuria. This was associated with a marked reduction in transfusion requirement. In two of the three transfused this was for reasons other than haematuria, namely blood product requirement for the underlying malignancy (lymphoma and myelodysplastic syndrome).

In summary, hyperbaric oxygen is an efficacious, well-tolerated, non-invasive and durable treatment option for radiation-induced haemorrhagic cystitis.

Limitations

Limitations of this study include a lack of objective assessment of measuring haematuria, and limited follow-up, both clinical and cystoscopic. There is no uniform duration of treatment, so patients receive a variable "dose" of hyperbaric oxygen.

Assessment of the efficacy of hyperbaric treatment should additionally be made with objective measurements. There is a need to do follow-up cystoscopy on all patients following treatment, particularly those with recurrent haematuria, to exclude recurrent malignancy or infection. Objective measurement of the amount of haematuria before, during and after treatment is desirable. Although the changes induced by hyperbaric treatment are assumed to be permanent, there is a place for long-term follow-up of these patients.

Experimentally the number of treatments required to induce long-term benefits (in terms of vascular density) has been determined, but this has yet to be defined in the clinical setting (and the end-point, namely, symptomatic improvement or resolution of haematuria, is different from vascular density), since a number of patients relapsed despite apparently adequate treatment duration, not significantly different from those who responded.

The treatment pressure (and therefore PO_2) and duration have not been universally agreed upon. Nonetheless, results from both this study and that of Weiss[1] using 2 ATA treatment pressure have results as efficacious (see Table 1) as those treating at higher pressures.[7,8,12] Assessment of the effect of varying pressure is difficult due to the wide variation in the number of treatments. These factors all represent opportunities for further clinical research, and there is a need for a standardised, prospective, multi-centre trial.

Currently, hyperbaric treatment is generally used only after a prolonged period of cystitis, or after other modalities has been used. Further studies are warranted to investigate the value of hyperbaric oxygen used earlier in the management of radiation-induced haemorrhagic cystitis, possibly even in prophylaxis. If this is so, it becomes even more important to identify those who are likely to develop radiation-induced haemorrhagic cystitis.

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THE WORLD AS IT IS

IMPROVING THE BUDDY SYSTEM

Sue Crowe

Key Words
Buddies, safety.

The ideal buddy system

Learner divers are told the "buddy system" is the best way to dive. But what exactly does having a buddy mean and is it the best system for all of us?

When I learnt to dive I was told that one should always dive with a buddy because:

your buddy checks your equipment and you theirs,
buddies keep an eye on each other,
your buddy is there when you need assistance and vice versa,
your buddy can save your life and you can do the same for them, and
having a buddy makes diving more fun.

In the PADI open water manual, the buddy system only rates one page and I quote,

"You should always dive with a buddy who stays nearby at all times. A buddy provides general assistance in putting on and checking your equipment before the dive; in helping remind you of your depth, time and air supply limits; and in giving you emergency assistance in the ***unlikely*** *event you need it. Your buddy will get the same assistance from you and both of you will feel more secure diving together than alone.*

"Diving is a social activity - diving with someone adds to the fun. Together you and your buddy will share experiences and witness the immense variety of scenes the underwater world displays. You may be surprised how many new friends you meet through diving and the buddy system.

"Keep in mind the three general reasons for diving with a buddy: 1) practicality, 2) safety and 3) fun. Remember you have a responsibility to your diving partner and that for the buddy system to work, you and your buddy must want it to work. Realise the need and value of the buddy system and decide now to always abide by it while diving."

Quite a responsibility. Most people do dive with a buddy. BUT during my diving years, the reality of the buddy system has been quite different.

The actual buddy system

For a start, if I am diving somewhere and I don't know anyone, I am usually buddied with a diver who I know nothing about. Once I was buddied with a diver, who, it turned out after I asked a few questions, did not even have a ticket!

Often, depending on which ticket I give the shop, I am buddied with a brand new diver and am expected to look after them and hold their hand. Most of the time this is fine but often I have to cut my dive short because my new buddy has run low on air or they are so nervous that I spend all my time watching them carefully and not enjoying the dive.

I have had buddies I have had to chase all over the dive site just to keep up and then they have the audacity to