Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis

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OBJECTIVE

To assess the efficacy of hyperbaric oxygen (HBO) for treating haemorrhagic cystitis.

PATIENTS AND METHODS

From February 1997 to April 2004, seven patients with radiation-induced haemorrhagic cystitis were treated with HBO; they received a mean (range) of 30 (18–57) HBO treatments and the follow-up was 24 (3–53) months.

RESULTS

The haematuria resolved completely in all seven patients shortly after treatment; one had an improvement but died from complications relating to cancer shortly after completing treatment, and two had recurrence of gross haematuria. They were re-treated with HBO until the haematuria resolved.

CONCLUSIONS

Radiation-induced haemorrhagic cystitis can be treated successfully with HBO primarily or after failure of standard regimens. This method was well tolerated even in patients debilitated by advanced cancer and blood loss. Long-term remission is possible in most patients, and re-treatment effectively manages recurrent bleeding.

KEYWORDS

hyperbaric oxygen therapy, radiation therapy, hemorrhagic cystitis

INTRODUCTION

Haemorrhagic cystitis can occur from 2 months to ≥10 years after pelvic irradiation. Levenback *et al.* [1] reported on 1784 patients who received radiotherapy for stage Ib cervical cancer over 29 years; haemorrhagic cystitis developed in 6.5%. Other studies reported an incidence of moderate to severe haematuria of 3–5% after radiotherapy for prostate cancer. The primary treatment for haemorrhagic cystitis is bladder irrigation; we initially start bladder irrigation with continuous saline, and the next step is cystoscopy and fulguration to stop bleeding bladder mucosa. If this treatment fails we initiate alum silver nitrate bladder irrigation. If all these methods fail we refer the patients for hyperbaric oxygen (HBO) therapy.

Oral and intravenous agents, e.g. aminocaproic acid, oestrogens and sodium pentosan polysulphate, have been tried with limited success. Intravesical treatments with alum silver nitrate, prostaglandins or formalin are sometimes used if bleeding persists. Finally, selective embolization of the hypogastric arteries, urinary diversion and cystectomy may be ultimately necessary in the most severe cases.

The potential clinical benefits of HBO have been reported for several decades. Among confirmed hyper- oxygenation physiological mechanisms operating in HBO are the induction of capillary angiogenesis and increased fibroblast concentration. These have also been established as micro-anatomical effects of HBO in irradiated tissues. HBO also induces healing of tissue damage, and decreases oedema, necrosis and leukocyte infiltration [2]. Recently HBO has emerged as a potential primary option for managing this challenging condition; we review our experience treating refractory haemorrhagic cystitis with HBO.

PATIENTS AND METHODS

Four men and three women (mean age 63 years, range 21–80) received HBO therapy for radiation-induced haemorrhagic cystitis. Ionizing radiation was administered for prostate cancer in the men, and metastatic breast cancer in one, cervical cancer in one and primitive neuro-ectodermal tumour (PNET) in the women. Radiation was given for local disease and the mean dosage delivered was 64 Gy.

Patients with haemoglobin levels of <80 g/L, cardiac debilitated patients with haemoglobin levels of <90 g/L and patients with a fast decline in haemoglobin levels received a blood transfusion. Stabilization was defined as three consecutive haemoglobin levels of >100 g/L in 24 h.

The interval from original radiation treatment to HBO therapy was 3–180 months; before therapy six patients had cystoscopy and biopsies to exclude malignancy. All random biopsies showed histological changes consistent with post-radiation cystitis. One patient had had a nephroureterectomy for upper tract TCC before the diagnosis of prostate cancer and radiotherapy. Cystoscopy, ureteroscopy, urine cytology and random biopsy were used to exclude an underlying disease.

HBO was administered at 0.2 MPa for 90 min daily in a walk-in multiplace hyperbaric

chamber; patients were monitored during the treatment. Five treatments were given weekly (on weekdays), with a mean (range) of 30 (18–57) treatments administered.

RESULTS

Of the seven patients, all had complete resolution or a marked improvement of haematuria after HBO therapy. Two patients had recurrence of haematuria and received 30 (in one) and 37 (in the other) additional treatments until the haematuria resolved. All patients but one had cystoscopy before HBO to exclude causes of bleeding other than haemorrhagic cystitis. These patients also had cystoscopy after HBO therapy, to visually assess the response to treatment, which revealed objective improvements in bladder mucosal appearance. One patient (the 21-year-old woman with PNET) had resolution of haematuria after 20 HBO treatments, but she died from her underlying disease 3 months after stopping the HBO treatment.

DISCUSSION

Radiation-induced tissue injury is the result of progressive endarteritis, leading to hypovascular, hypocellular and hypoxic tissue (the 'three-H' tissue). The ability to replace normal collagen and cellular loss is compromised, resulting in tissue breakdown, and once irradiated tissue breaks down it is unlikely that it will heal [3]. Gross haematuria caused by the breakdown of bladder mucosa and damaged pathological blood vessels in the bladder wall may ensue weeks or decades after irradiation therapy. Cystoscopy findings reveal patchy diffused bleeding ulcers in the bladder.

Technically, the delivery of HBO therapy occurs when the patient rests the whole body and breathes 100% oxygen in a treatment chamber which is above atmospheric pressure, e.g. >0.1 MPa (absolute atmospheric pressure, AA). Pressurization at 1.4–3 times AA while the patient inhales oxygen meets the Undersea and Hyperbaric Medicine Society definition of HBO treatment [4].

The hyperbaric chamber provides conditions in which a very high dose of oxygen may be administered to the tissue. In these conditions the haemoglobin is fully saturated and the oxygen dissolved in the blood plasma at the rate of 2.3 volume percentage of hyperoxaemia per 0.1 MPa AA. This amount of hyperoxygenation cannot be achieved by any other means available in medical practice. These high doses of oxygen promote physiological mechanisms that have clinical affects in different pathological conditions, e.g. impaired oxygen delivery or impaired oxygen metabolism. HBO is considered an adjunctive treatment to medical and surgical care, as in acute traumatic ischaemic injury. HBO treatment has been shown to reduce oedema and enhance aerobic metabolism [5–7]. HBO may also facilitate the transport of some antibiotic agents across the bacterial cell wall, thus improving their overall effectiveness [8]. In addition, hyperoxaemia improves collagen formation, fibroblast growth and angiogenesis, which also enhance wound healing.

At the joint consensus meeting of the European Society for Therapeutic Radiation and Oncology and the European Committee for Hyperbaric Medicine (Lisbon, 2001) it was established that according to evidence-based medicine criteria, the effect of HBO treatment on angiogenesis and osteogenesis in irradiated tissue is graded as level 1 [9].

The therapeutic effects of HBO for the treating long-term radiation effects were initially described by Marx and Ames [10] for post-irradiated head and neck cancer. Marx [3] redefined the sequence of the pathogenesis of radionecrosis as 1 (radiation), 2 (hypoxic-hypocellular-hypovascular tissue), 3 (tissue breakdown) and 4 (chronic non-healing wound). Beneficial effects of HBO on radiation-damaged tissue are related to the hyperoxia-induced primary neovascularization and secondary growth of healthy granulation tissue [11,12]. Additional benefits include vasoconstriction, which may help in reducing oedema, and improvements in wound healing and immune function [12–14].

HBO therapy enhances healing in a variety of radiation-injured tissues [12]. In an animal model, breathing 100% oxygen at normal atmospheric pressure produced no effect on angiogenesis in irradiated tissues. However, HBO at 2.4 AA produced an 8–9-fold increase in vascular density in irradiated tissues over normobaric oxygen and air-breathing controls. This stimulus for angiogenesis appears to be mediated at least partly through tissue macrophages responding to the steep oxygen gradient achieved in the hyperbaric environment [15]. Follow-up for up to 4 years after HBO therapy showed that transcutaneous oxygen measurements remain near normal levels, implying that the angiogenesis is essentially permanent [16].

Case series of radiation-induced haemorrhagic cystitis treated with HBO have been reported [17–29]; despite differences in the number of HBO treatments administered and characteristics of hyperbaric exposure among the various reports, most authors concluded that HBO therapy is effective for intractable radiation-induced haemorrhagic cystitis. If the earlier case series reported are combined, 82% of patients treated with HBO had an improvement or resolution of haematuria. The response to HBO depended on the severity of the presenting haematuria.

Although various authors reported a positive response to HBO for treating radiation-induced haemorrhagic cystitis the duration of follow-up varied. Del Pizzo *et al.* [25] reported on 11 patients treated with 28–64 HBO treatments and followed for a mean of 5.1 years. At a mean follow-up of 2.5 years eight of 11 patients were asymptomatic, while at 5.1 years five of the remaining eight had recurrent haematuria requiring hospitalization, blood transfusion and ultimately supravesical urinary diversion. Of these five patients two eventually required embolization and cystectomy. Of the 11 patients, three had a complete and durable resolution of symptoms at a mean of 5 years. This study highlights the progressive nature of radiation injury. The possibility that repeat HBO treatments might provide additional benefit has not been explored in detail. Investigators at Duke University analysed all published series and found that 40 HBO treatments was the optimum for acute resolution of symptoms and a long-term durable result [30].

The potential side-effects of HBO therapy are usually well tolerated. Some diabetic patients may have an exaggerated hypoglycaemic response to hyperoxia, the mechanism of which is yet to be defined. To minimize these side-effects, the patients' glucose level should be monitored. Patients with emphysema, a history of spontaneous pneumothorax and any other obstructive pulmonary disease should be closely monitored. CNS or pulmonary oxygen toxicity is unlikely in HBO treatment, which does not expose the patient to those oxygen side-effects.

In conclusion, haemorrhagic cystitis is a debilitating complication of radiation therapy for pelvic malignancy. Standard therapeutic methods have limited success and may have significant side-effects. HBO therapy is safe and noninvasive for treating the underlying histological changes that occur with radiation injury, resulting in long-term complete resolution in a large proportion of patients in whom standard treatment regimens fail. Early institution of HBO results in rapid resolution of haematuria. HBO therapy should be added as a preferred option for treating persistent haemorrhagic cystitis.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **HBO**, hyperbaric oxygen; **AA**, absolute atmospheric (pressure); **PNET**, primitive neuro-ectodermal tumour.