



Hyperbaric oxygen for radiation injury: is it indicated?

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The article by Craighead *et al.* in this issue of *Current Oncology* presents a systematic review of the use of hyperbaric oxygen (HBO2) to treat delayed pelvic radiation complications in patients with gynecologic cancer. The authors are oncologists and hyperbaric specialists from several well-known medical centers across Canada. Their stated purpose is to provide guidance for the application of HBO2 to delayed radiation injuries such as cystitis, proctitis, soft-tissue and bony necrosis, and other miscellaneous complications. To accomplish their goals, they completed a systematic search using standard electronic search engines and appropriate keywords. They ultimately report thirteen publications, including two randomized controlled trials. Feedback from an external review panel was sought and incorporated into the preparation of their paper. Consensus was achieved through an informal vote.

Reports of HBO2 in the treatment of delayed radiation complications date back to the mid-1970s¹. The reports have been almost universally positive, but the level of evidence has been low, with most reports consisting of uncontrolled case series. The authors of the current publication include two randomized controlled trials that show efficacy for HBO2 in the treatment of late complications after pelvic radiation.

Delayed radiation injury (soft-tissue and bony necrosis) is one of the entities included as an approved indication in the Hyperbaric Oxygen Therapy Committee Report of the Undersea and Hyperbaric Medical Society². The Undersea and Hyperbaric Medical Society is the largest international professional society for HBO2 practitioners. The European radiation oncology and hyperbaric medicine communities convened a consensus conference in 2001 and determined by juried vote that there was adequate evidence to support the use of HBO2 in the treatment of radiation-induced injuries, especially mandible necrosis and hemorrhagic cystitis³. Feldmeier *et al.*⁴ completed a systematic review of HBO2 in the treatment of delayed radiation injuries, and Bennett *et al.*⁵ completed a Cochrane review. Both of those publications support HBO2 in the treatment of radiation injury, although

the Cochrane review, with its emphasis on randomized controlled trials, does not advocate universal application of HBO2 to delayed radiation injuries. In the United States, third-party insurance entities will frequently reimburse for this application, but often a formal appeal will be required to obtain payment. In informal surveys of HBO2 practitioners at continuing medical education meetings on hyperbaric oxygen, I have consistently found that between one third and one half of U.S. patients treated with HBO2 are treated for delayed radiation injuries.

A landmark development in the science supporting HBO2 for radiation injury is the publication, in the *International Journal of Radiation Oncology*, of the results of a randomized trial for patients with radiation proctitis. This multi-institutional blinded trial was sponsored by the Baromedical Research Foundation (<http://www.baromedicalresearch.org>). That foundation is in the process of completing similar studies in radiation injury (called the Hyperbaric Oxygen Radiation Tissue Injury Study) including osteoradiation necrosis, soft-tissue radiation necrosis, laryngeal radiation necrosis, radiation-induced cystitis, and gynecologic injuries. Another study in the same series will examine the role of HBO2 in the prevention of serious injuries.

Craighead *et al.* conclude that

- HBO2 is likely effective for this indication.
- HBO2 should be applied in refractory disorders.
- HBO2 may provide symptom resolution in certain complications of radiation.
- HBO2 may reduce complications when combined with surgery removing tissues and organs affected by necrosis.

I am in complete agreement with the authors. Their review is well done, and the conclusions that they draw in support of HBO2 application are conservative. Radiation complications are fortunately fairly rare, with most radiation oncologists willing to accept a 5% serious complication rate when treating with curative

intent. When serious radiation complications do occur, no effective treatment other than resection of the affected tissues is known. Surgical interventions may be poorly tolerated and are certainly not desirable in a group of patients who have already completed a course of treatment for their cancer that may have included surgery, radiation, and chemotherapy. Hyperbaric oxygen is a very safe therapy; its serious complications occur in fractions of a percentage point. It is not uncommon for patients to have myopic visual changes, but these are usually temporary. Treatments with HBO2 are expensive, but much less so than some of the newer cancer therapies, including intensity-modulated radiation therapy and the newer chemotherapy agents and marrow growth factors.

The authors include a brief discussion of the mechanisms by which HBO2 is felt to be effective in delayed radiation injury. The effects of HBO2 on angiogenesis are prominently discussed, and those effects are certainly part of the positive therapeutic effect of HBO2 in that setting. Most recently, the radiation oncology community has focused on fibrosis and depletion of stem cells as prominent features in delayed radiation injury. These features have been termed the “fibro-atrophic effect.” A recent exciting study from Thom *et al.*⁶ demonstrates that HBO2 can mobilize stem cells from bone marrow after irradiation. Articles by Feldmeier and colleagues have shown by quantitative morphometry that HBO2 can reduce fibrosis in an animal model of radiation enteritis^{7,8}. It is likely that the effects of HBO2 are multiple.

Craighead *et al.* discuss the issue of whether HBO2 poses a potential risk for cancer recurrence. They recommend that patients be cancer-free before initiating a course of HBO2. I agree with that recommendation. In gynecologic injuries especially, it is often difficult to distinguish between pure radiation injury and tumour recurrence. When a recurrent cancer is present, HBO2 will not offer any positive therapeutic effect. However, in a systematic literature review, Feldmeier and colleagues⁹ examined animal and clinical studies, including the large randomized controlled trials from the era of HBO2 applied as a radiosensitizer, and found that nearly all of those articles showed no evidence to support concerns that HBO2 was leading to an increase in tumour recurrence.

CONFLICT OF INTEREST DISCLOSURES

JJF has no financial relationship with any pharmaceutical companies, nor does he hold any stock investment in such companies. He is the President-elect of the Undersea and Hyperbaric Medical Society and as such is a member of that society's board of directors.

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