Hyperbaric Oxygen therapy for radiation necrosis of the jaw: Comments on a randomized study.

To the Editor:

Systematic studies in both animals (1) and humans (2), and several years of clinical experience (3) have provided strong evidence that hyperbaric oxygen (HBO$_2$) largely reverses the hypovascularity in late radiation injury and leads to improved outcomes in mandibular osteoradionecrosis. Nevertheless, few randomized trials have thus far been performed.

In a recently published article, Annane and colleagues have attempted to fill this void by reporting the results of a prospective, randomized double-blind multi-center trial of HBO$_2$ therapy in osteoradionecrosis (ORN) of the jaw (4). The authors enrolled 68 patients; 31 were randomized to receive HBO$_2$ (100% O$_2$ at 2.4 ATA for 90 minutes 5 days per week), 37 to receive placebo (9% O$_2$ under the same conditions). The patients were classified into two groups: group A had areas of exposed bone <20 mm in diameter, no cutaneous fistula and no a priori need for surgery; group B had areas of exposed bone >20 mm in diameter, cutaneous fistula or an a priori need for surgery. The authors defined recovery as: absence of pain, absence of any area of bone exposure, stabilization or regression of radiographic abnormalities and absence of treatment failure (at least one of: fracture, bone reabsorption to the inferior border of the mandible, cutaneous fistula or need for surgery in group A patients). The statistical analysis was on the basis of intention-to-treat.

At one year follow-up there was no significant difference in the number of patients who had recovered (6 of 31 in the HBO$_2$-treated group, vs. 12 of 37 in the placebo group). Forty-two patients (20 in the HBO$_2$-treated group, 22 in the placebo group) eventually underwent surgery, preceded by 10 additional hyperbaric treatments (HBO$_2$ or placebo). The subsequent recovery rates after initial surgery were 17/20 (85%) HBO$_2$-treated patients vs. 17/22 (77%) sham-treated patients; after a second operation the recovery rates were 17/20 and 20/22 patients in each arm. The authors concluded that hyperbaric oxygen should not be recommended for patients with overt mandibular osteoradionecrosis in the absence of fracture or bone resorption to the inferior border.

Welcome as a randomized trial is in this area, this study unfortunately falls short. The study design was not consistent with the current standard of care of these patients in
the US, which is a multimodality approach combining prophylactic HBO₂, surgery and follow-up HBO₂ (5). The treatment plan for the non-surgical treatment group (group A) is inconsistent with the standard of care promulgated by most clinicians. Longstanding clinical experience with ORN indicates that after HBO₂ treatment, while symptoms sometimes resolve, and gingival defects can re-epithelialize, the underlying disease process remains (necrotic bone remains dead), and relapse rates are high. It is well-recognized that neither conservative treatment nor HBO₂ will revitalize dead bone (6), hence the need for a priori surgical debridement following an initial course of HBO₂. The high percentage of patients in Annane’s series who ultimately required surgery even within one year confirms this notion. Although it is reported that a significant fraction of the patients in group A (HBO₂-treated and placebo) had recovered at one year, it would be contrary to the natural history of the disease if many of these remained that way in the long term, or indeed that any achieved both clinical and radiographic resolution.

The study also highlights a number of important conceptual misunderstandings about the treatment of ORN. Although all patients in the HBO₂ group in Annane’s study received at least one HBO₂ treatment, the authors do not report the full range of the number of HBO₂ sessions, it is possible to discern that one quarter of their patients received fewer than 22 HBO₂ treatments. Thus, for some patients in the series, the number of HBO₂ treatments could have been too low to have achieved the desired effect of HBO₂: increased soft tissue capillarity, and improved wound-healing in irradiated tissue. The failure to administer HBO₂ in the recommended dose to a significant number of patients in the experimental group undermines the study’s statistical validity and applicability to clinical practice.

We are therefore left with a subgroup of fewer than 42 patients in two groups, who had undergone surgery preceded and followed by the recommended number of HBO₂ treatments, and thus in whom it could be appropriate to compare the effectiveness of adjunctive HBO₂. The authors did not specifically report the clinical baselines of this subgroup of the larger study population, rendering it difficult to interpret the outcome. However, even if taken at face value, based on the authors’ own power analysis this number is considerably fewer than would be required to exclude a significant effect of HBO₂.

Finally, intention-to-treat analysis is entirely appropriate for a study with a positive outcome, in order that a treatment effect not be overvalued by an unrealistic estimate of patient compliance in clinical practice. However, in this case the effect of the intention-to-treat analysis is to erode their conclusion that HBO₂ is ineffective in ORN. A simpler explanation for the negative result is lack of statistical power.

We fully agree with the need for randomized controlled trials of expensive, time consuming modalities such as hyperbaric oxygen for the treatment of osteoradionecrosis. But we feel that the study of Annane et al. does not attain the level of evidence required to alter the standard of care, which is surgical debridement or reconstruction preceded by 30 HBO₂ treatments and followed by 10 more.

Richard E. Moon, MD
Departments of Anesthesiology and Medicine
Center for Hyperbaric Medicine and Environmental Physiology
Duke University Medical Center, Durham, NC

Thomas A. McGraw, DMD
Division of Plastic, Reconstructive, Maxillofacial and Oral Surgery
Duke University Medical Center, Durham, NC
George Blakey, III
Department of Oral and Maxillofacial Surgery
University of North Carolina at Chapel Hill,
Chapel Hill, NC

REFERENCES