

Letter to the Editor

In response to the negative randomized controlled hyperbaric trial by Annane et al in the treatment of Mandibular ORN.

To the Editor:

The recent paper by Annane et al (1) is initially quite disturbing and surprising for those of us who have experienced the consistent clinical benefit of hyperbaric oxygen (HBO₂) in the treatment of delayed radiation injuries (soft tissue and bony radiation necrosis). However, a careful reading of the paper raises concerns with the treatment protocol as designed and ultimately reported by these well-intentioned authors. Instead of answering the useful clinical question, “Does the addition of hyperbaric oxygen to an aggressive multidisciplinary treatment protocol result in improved outcome,” they have confirmed the already known answer to the question, “Does hyperbaric oxygen in the absence of a multidisciplinary approach obviate the need for complete surgical debridement?” In a 1984 review of the United States Air Force experience with hyperbaric oxygen, and prior to developing his staged multidisciplinary approach, Marx reported a success rate of 26% in achieving bone coverage (2). This success rate is remarkably similar to that reported in the Annane paper of 19% in the hyperbaric group.

Interestingly, the authors offer no explanation as to why patients in the placebo arm had a higher rate of recovery of 32%.

The oncology community and physicians in general are well aware of the value of multidisciplinary therapy in the treatment of cancer patients. In multidisciplinary treatments, every aspect of treatment must be optimized to ensure the best chances for positive outcome. In a combined modality protocol, if the surgical component is inadequate, it is axiomatic that adjuvant radiation or chemotherapy is destined to fail. Such a poorly designed protocol when reported would not disprove the value of adjuvant therapies. Instead, it would reinforce the need for optimized surgery. Prior to Dr. Robert Marx’s design and popularization of a formal staging system and treatment protocol of the mandible, the experience with hyperbaric oxygen for osteoradiation necrosis (ORN) was only rarely successful (2). Many patients who had failed “conservative treatment” subsequently underwent prolonged courses of treatment (sometimes more than 100 hyperbaric treatments) with, usually, only a temporary palliation of symptoms but almost never a durable resolution of their ORN. Only with surgical extirpation of all necrotic bone will the process of mandibular osteoradionecrosis be successfully arrested. In this manuscript, surgical intervention is not well described. Never do the authors indicate that

their goal was to surgically extirpate all dead bone. This principle is an absolute requirement for successful outcome in ORN. In fact, in correspondence with one of the undersigned (MB), Professor Annane writes that he considers the need for surgery to be indicative of failure of the hyperbaric oxygen. In the Marx experience, not only is surgical extirpation of necrotic bone proven to be essential for success, but in about two thirds of patients a mandibular resection resulting in discontinuity and reconstruction are necessary to achieve successful resolution of the ORN with good functional and cosmetic result.

A previous manuscript reporting the results of hyperbaric oxygen in the treatment of chest wall necrosis with hyperbaric oxygen confirmed the prior extensive mandibular experience. These authors also found that only after adequate debridement and removal of necrotic bone could they expect durable resolution of radiation-induced chest wall ORN (3).

Marx (2) assessed the results of the early publications reporting hyperbaric oxygen as a treatment for ORN and based on his own early experiences while at Wilford Hall USAF Medical Center in the late 1970's and early 1980's established a treatment protocol for ORN that is unexcelled to this day. The treatment protocol followed along formalized lines predicated on the staging system he developed. Stage 1 patients have small amounts of necrotic bone usually debrided adequately in the dental chair. If patients fail treatment in Stage 1, they are advanced to Stage 2 and have formal surgical debridement in the operating room. Stage 3 patients are those who have grave signs such as fistulae, pathologic fractures or extension of the necrosis to the inferior margin of the mandible. Stage 2 patients who fail to respond to treatment at this level are also advanced to Stage 3. These patients have planned mandibular resections with a discontinuity defect, which is addressed

with a planned reconstruction. All patients in all stages have 30 pre-operative daily hyperbaric treatments for 90 minutes of 100% oxygen at 2.4 atmospheres absolute pressure followed by 10 post-operative treatments. Those patients requiring reconstruction return at a later date and following reconstruction undergo 10 additional hyperbaric treatments.

Besides the failure to extirpate necrotic bone aggressively and completely, in the Annane publication, the investigators delivered hyperbaric oxygen in a non-standard fashion, i.e. two treatments per day. The vast majority of hyperbaric centers treat radiation necrosis one treatment per day as per the Marx protocols. Only one major hyperbaric center in the United States utilizes a twice per day treatment regimen for radiation injuries.

In a review article by Feldmeier and Hampson (4), the authors recently summarized the published international and multi-institutional experience in the treatment or prevention of ORN with a multi-disciplinary approach that includes hyperbaric oxygen. Only one of the 13 publications reviewed was negative for an advantage for hyperbaric oxygen while the other 12 show a strong positive effect of hyperbaric oxygen. This only prior negative trial failed to heed Dr. Marx's determination that hyperbaric oxygen should be initiated and the majority delivered prior to any surgical intervention.

The authors' efforts to accomplish a randomized controlled trial of hyperbaric oxygen in the management of ORN are applauded. Unfortunately, they failed to recall the pre-Marx experience and adopt the Marx protocol in its entirety. A series of randomized controlled studies titled the HORTIS (Hyperbaric Oxygen for Radiation Tissue Injuries Study) trials are underway sponsored by the Baromedical Research Institute. These protocols adhere to a study design which includes the optimization of all aspects of treatment. We anxiously await

these results. In the interim, for those who seek to treat ORN in a multidisciplinary fashion, recall the importance of several principles established by Marx and confirmed by many additional clinicians/authors:

1. Deliver the majority of HBO₂ prior to any surgical wounding to improve the vascular milieu of these wounded tissues before the surgical insult.
2. Eradicate *all* non-viable bone even if a segmental mandibular resection and ultimate reconstruction are required.
3. Optimize surgical technique in all aspects to employ the use of modern reconstructive surgical procedures including microvascular anastomoses, free flaps and the rotation of myocutaneous flaps when needed to replace tissues lost as a result of accompanying soft tissue necrosis or the original cancer resection.

For the reasons given above, the Annane study fails to assess the role of hyperbaric oxygen in the appropriate and appropriately sequenced multi-disciplinary treatment of mandibular osteoradionecrosis. Only if and when all other aspects of treatment are delivered in an optimal fashion can the impact of hyperbaric oxygen be critically evaluated.

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