VOLUME 22 · NUMBER 24 · DECEMBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hyperbaric Oxygen Therapy for Radionecrosis of the Jaw: A Randomized, Placebo-Controlled, Double-Blind Trial From the ORN96 Study Group

Djillali Annane, Joël Depondt, Philippe Aubert, Maryvonne Villart, Pierre Géhanno, Philippe Gajdos, and Sylvie Chevret

From the Unité de Médecine Hyperbare and Service Pharmaceutique, Hôpital Raymond Poincaré, Garches; Service ORL et Chirurgie Cervico-Faciale Hôpital Bichat-Claude Bernard; and Département de Biostatistique et Informatique Médicale, Hôpital Saint Louis, Paris, France.

Submitted September 3, 2003; accepted June 29, 2004.

Supported by a grant from the French Ministry of Health, PHRC AOM95211.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Djillali Annane, MD, PhD, Service de Réanimation Médicale-Hôpital Raymond Poincaré (AP-HP), Université de Versailles Saint Quentin en Yvelines, 104 Boulevard Raymond Poincaré, 92380 Garches, France; e-mail: djillali.annane@rpc.ap-hop-paris.fr.

0732-183X/04/2224-4893/$20.00

DOI: 10.1200/JCO.2004.09.006

ABSTRACT

Purpose
To determine the efficacy and safety of hyperbaric oxygen therapy (HBO) for overt mandibular osteoradionecrosis.

Patients and Methods
This prospective, multicenter, randomized, double-blind, placebo-controlled trial was conducted at 12 university hospitals. Ambulatory adults with overt osteoradionecrosis of the mandible were assigned to receive 30 HBO exposures preoperatively at 2.4 absolute atmosphere for 90 minutes or a placebo, and 10 additional HBO dives postoperatively or a placebo. The main outcome measure was 1-year recovery rate from osteoradionecrosis. Secondary end points included time to treatment failure, time to pain relief, 1-year mortality rate, and treatment safety.

Results
At the time of the second interim analysis, based on the triangular test, the study was stopped for potentially worse outcomes in the HBO arm. A total of 68 patients were enrolled and analyzed. At 1 year, six (19%) of 31 patients had recovered in the HBO arm and 12 (32%) of 37 in the placebo arm (relative risk = 0.60; 95% CI, 0.25 to 1.41; $P = .23$). Time to treatment failure (hazard ratio = 1.33; 95% CI, 0.68 to 2.60; $P = .41$) and time to pain relief (hazard ratio = 1.00; 95% CI, 0.52 to 1.89; $P = .99$) were similar between the two treatment arms.

Conclusion
Patients with overt mandibular osteoradionecrosis did not benefit from hyperbaric oxygenation.

J Clin Oncol 22:4893-4900. © 2004 by American Society of Clinical Oncology

INTRODUCTION

The mandible is the most common site of radiation-induced tissue damages following treatment of head and neck cancer,[1] with an incidence of 5% to 15% of cases.[2] The underlying mechanisms include radiation-induced hypoxia and ischemia resulting in imbalance between cell death and cell replacement, and between collagen degradation and synthesis.[3] It was recently suggested that osteoradionecrosis may be triggered by a predominantly fibro-atrophic mechanism.[4] In theory, hyperbaric oxygen therapy (HBO) may stimulate monocytes and fibroblasts function and collagen synthesis,[5,6] and may increase vascular density.[7] In practice, uncontrolled studies showed recovery rates from osteroradionecrosis of 15% to 45% with HBO alone, and 20% to 90% with HBO combined to surgery.[1,8] However, its wide use to treat patients with osteoradionecrosis is not yet supported by well-designed randomized clinical trials.[9] In 74 patients who needed dental management after radiation therapy for head and neck cancer,

HBO (20 sessions before and 10 sessions after tooth removal) plus perioperative penicillin were compared to perioperative penicillin alone.[10] Two of 37 patients in the HBO group and 11 of 37 in the penicillin group developed mandibular osteoradionecrosis ($P = .005$). A second trial has compared two doses of HBO (2 absolute atmosphere [ATA] versus 1.2 ATA oxygen therapy) in 12 patients with overt osteoradionecrosis. However, the authors failed to provide quantitative data on which one can estimate treatments effects.[11]

Therefore, the current trial was aimed at evaluating the efficacy and safety of HBO for the treatment of overt mandibular osteoradionecrosis.

PATIENTS AND METHODS

From October 1997 through November 2001, all consecutive eligible patients were enrolled in this randomized, double-blind, placebo-controlled trial, which was conducted at 12 contributing centers in Paris and its suburbs. The protocol was approved by an ethics committee and written informed consent was obtained from all patients. An independent safety and efficacy monitoring board (SEMB) oversaw risks and benefits during formal interim analyses.

Patients

Consecutive patients were admitted at one of the 12 contributing centers. Patients with past history of radiation and with overt mandibular osteoradionecrosis were included in the study if they had (at least 2 months after optimal conservative treatment, including antibiotics, local irrigation, and surgery): (1) one of the following clinical criteria: pain, dysesthesia in the distribution of the inferior alveolar nerve, areas of bone exposure, trismus, fistula; and (2) one of the following radiographic criteria: increased density, periosteal thickening, diffuse radiolucency, mottled areas of osteoporosis, and sclerosis sequestration. Exclusion criteria included fracture or radiographic evidence of bone reabsorption to the inferior border, ongoing cancer, previous treatment with HBO, or contraindication to HBO (eg, emphysema, uncontrolled asthma or epilepsy, and/or previous optic neuritis).

Before randomization, eligible patients were graded by the same surgeon (P.A.) in group A: areas of exposed bone < 20 mm in diameter, no cutaneous fistula, and no a priori need for surgery; and in group B: areas of exposed bone of > 20 mm, cutaneous fistula, or an a priori need for surgery.[7]

Randomization

The random allocation sequence (1:1) was generated by the statistician and stratified on the patient's group (A or B) and center using a computer-generated list equilibrated every four patients. Patients were assigned to their treatment group by the pharmacist, and the allocation sequence remained concealed for all investigators, patients, nursing staff, and the members of the SEMB throughout the study period.

Study Treatments

HBO was performed using a multiplace chamber (CXPRO; COMEX, Marseilles, France) pressurized with compressed air, and, at plateau, the patients received, via a tight-fitting oronasal mask, either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (the placebo), which yielded similar arterial oxygenation than breathing room air at 1 ATA. Patients in group A were randomly assigned to receive daily HBO exposures (ie, a total of 30 exposures) at 2.4 ATA for 90 minutes each time, 5 days a week for 3 consecutive weeks, or the placebo. Patients in group B were similarly randomly assigned to receive 30 HBO exposures before undergoing a surgical cure and 10 additional HBO exposures 1 to 3 weeks after surgery, or the placebo. Patients in group A who had progressed to group B also received 10 additional HBO dives postoperatively, or the placebo. During each hyperbaric session, recordings of the actual fraction of inspired oxygen delivered to the patients was checked by the pharmacist in order to ensure that the patients were receiving the treatment to which they were assigned. In addition, the actual arterial oxygen tension achieved at 2.4 ATA plateau was recorded during the patient's first dive.

Conservative treatments included, in all cases, analgesics, the combination of amoxicilline-clavulanate, and a quinolone, debridement/curettage plus irrigation. Patients in group B (either at randomization or those who progressed from group A to group B during follow-up) had, whenever appropriate, transalveolar sequestrectomies, labial or lingual mucoperiosteal flaps, closure of cutaneous fistula or reconstruction of large soft tissue losses, or segmental resection with microvascular reconstruction.

Data Collection at Inclusion

Clinical evaluation. The following data were recorded : (1) general characteristics including age and sex, the Karnofsky performance status, comorbidities, (ie, hypertension, diabetes, diffuse atherosclerosis); (2) the past history of cancer, including site and histologic type of tumor and tumor-node-metastasis system grade; (3) the past history of radiation including the technique of irradiation (ie, implants or external treatments), the dates, duration, and total dose delivered to the patient; and (4) the history of radionecrosis including causing factors, signs at onset and at inclusion, and previous treatments (ie, antibiotics and surgery—types and dates).

Laboratory variables. The chest x-ray, a computed tomography scan of the mandible, and routine hematologic and chemistry data were systematically obtained.

Follow-Up

The following data were recorded monthly by the patient's primary physician during the 1-year period following random assignment: vital signs, head and neck examination, and results from standard laboratory tests. An x-ray or computed tomography scan of the mandible was scheduled to be performed at 6 months and at 1 year, or whenever necessary. All study outcomes were blindly assessed by the same surgeon (P.A.).

Outcomes

The primary outcome was the number of patients who had recovered from osteoradionecrosis at 1 year. Recovery was defined by: (1) absence of pain, (2) absence of any area of bone exposure, (3) stabilization or regression of radiographic findings, and (4) absence of treatment failure, which was defined by at least one of the following criteria: occurrence of fracture, bone reabsorption to the inferior border of the mandible, and cutaneous fistula or need for a surgical cure for patients in group A. Secondary outcomes included time to treatment failure, time to pain relief, 1-year mortality rates, and treatment safety. All study outcomes were blindly assessed by the same surgeon (P.A.).

Sample Size—Stopping Rules

Assuming a 1-year recovery rate of 10% in the control group,[5,12] and controlling for a type I error and a type II error of

5% each, a sample size of 222 patients had to be recruited to detect a difference with HBO of at least 20%. Owing to ethical concerns and to the uncertainties around actual treatment benefit, interim analyses based on the triangular test were scheduled after inclusion of every 30 patients, with computation of Z and V statistics from the accumulated data. Positive values of Z indicate superiority of the experimental treatment, zero values indicate equivalence, and negative values inferiority, while V is a measure of information in the trial. Once Z and V were computed, they were plotted against one another and the resulting point compared with stopping boundaries.[13]

It was decided a priori that the study would be stopped prematurely for safety concerns and evidence for HBO superiority or futility.

Statistical Analysis

The statistical analysis was based on the intent-to-treat principle. Estimation of 1-year recovery rates was defined by the ratio of observed recoveries to the total number of randomly assigned patients. Recovery rates were compared by χ^2 tests, with estimated unadjusted relative risk (RR) of recovery (and 95% CIs). Mantel-Haenszel tests allowed stratification on baseline severity group (ie, group A and group B). Time to treatment failure and time to pain relief within the first year following randomization were estimated using the Kaplan-Meier method,[14] and compared between treatment arms by the log-rank test.[15] Regression Cox models allowed to test for proportional hazards assumption, as well as to search for prognostic covariates and to test for interaction between randomization and covariates.[16] Estimated hazard ratio of failure and 95% CIs were computed.

Statistical analysis was performed on SAS 8.2 (SAS Institute, Cary, NC) and Splus2000 (MathSoft, Seattle, WA) software packages. All tests were two-sided, with *P* values of .05 or less denoting statistical significance.

RESULTS

The second interim analysis (reference date, March 25, 2001) based on the first 60 patients showed that the second point in the triangular test crossed the lower boundary, concluding lower recovery rates in the HBO arm when compared to the placebo arm (Fig 1). Then, the independent SEMB advised stopping enrollment. Results presented included data from eight additional patients whose follow-up period ended after the second interim analysis.

Baseline Characteristics of the Patients

From October 1997 to March 2001, 134 patients with a past history of irradiation for head or neck cancer were referred to the hyperbaric unit for radionecrosis. Sixty-six patients failed to meet at least one eligibility criteria. Sixty-eight patients were eligible, 31 in the HBO arm and 37 in the placebo arm (Fig 2). At baseline, the demographic characteristics, past history of cancer, and the characteristics of mandibular radionecrosis were similar on average in the two treatment arms (Table 1).

Outcome Measures

Among the 68 randomly assigned patients, at 1 year there were six (19.3%) of 31 patients who had recovered in the HBO arm and 12 (32.4%) of 37 in the placebo arm (RR = 0.60 ; 95% CI, 0.25 to 1.41; $P = .23$). Stratifying on baseline severity group slightly modify these results (RR = 0.58; 95% CI, 0.25 to 1.38; $P = .21$).

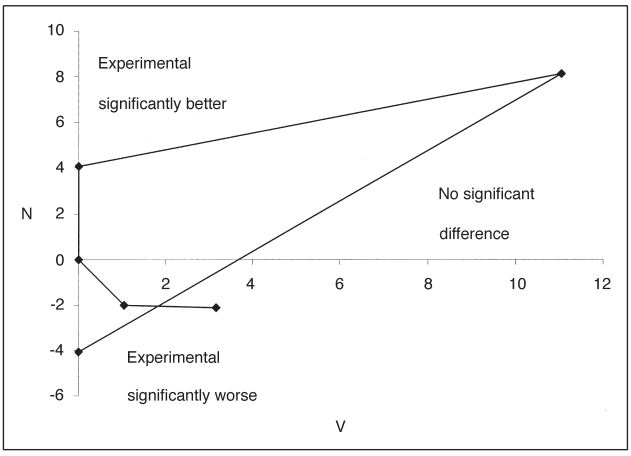

Fig 1. Stopping boundaries for sequential monitoring (triangular test), computed from type I error (5%) and power (95%) requirements, and treatment benefit to be detected (20%). The trial ended at the second inspection, with the lower boundary crossed (worse recovery rates in the hyperbaric oxygen therapy arm).

Of the 50 patients who had not recovered at 1 year, 34 had previously experienced treatment failure. The estimated hazard ratio (HR) of failure was 1.33 (95% CI, 0.68 to 2.60; $P = .41$). This result was not modified by adjusting for baseline severity group ($P = .42$).

At follow-up, a total of 28 patients had ulcerations, 13 in the HBO arm and 15 in the placebo arm ($P = .98$). The median diameter of the main lesion was 30 mm (first and third quartiles, 20 to 30 mm) in the HBO arm and 15 mm (first and third quartiles, 10 to 30 mm) in the placebo arm ($P = .06$ by the Wilcoxon rank sum test). Overall, 14 patients had bone sequestra, seven in each treatment arm.

Of the 54 patients in stage A at enrollment, 26 (48.1%) progressed to stage B, 14 (56%) of 25 in the HBO arm and 12 (41.4%) of 29 in the placebo arm ($P = .41$). Six patients (8.8%) underwent segmental resection and microvascular reconstruction (three in each treatment arm [$P = .99$]), and 18 patients (26.5%) were operated on for mandibular fracture with subsequent microvascular reconstruction (nine in each treatment arm [$P = .78$]).

Forty-two patients (61.8%; 20 in the HBO arm and 22 in the placebo arm) were eventually operated on. The subsequent recovery rates were 17 (85%)of 20 patients in the HBO arm and 17 (77.3%) of 22 patients in the placebo arm ($P = .70$) after a first surgery. After a second surgery, the recovery rates were 17 (85%) of 20 patients and 20 (90.9%) of 22 patients ($P = .66$) in the HBO and placebo arms, respectively.

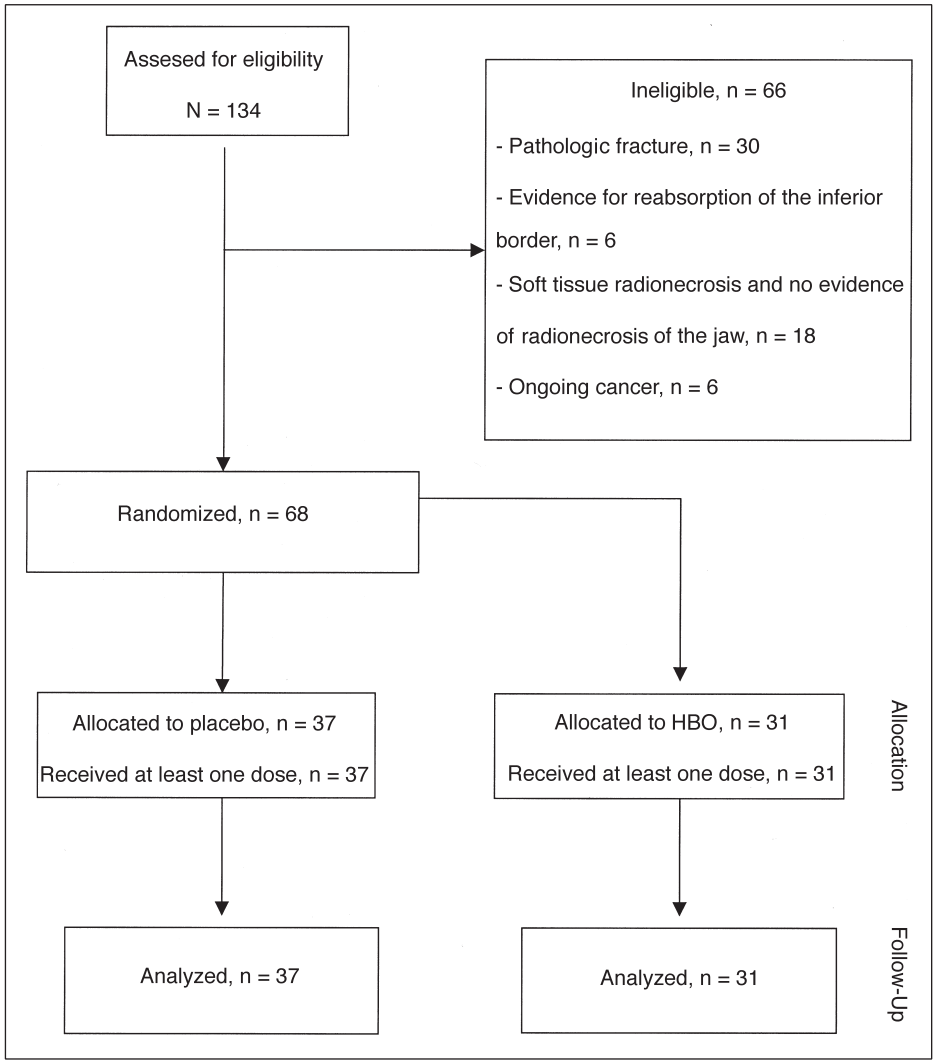

Fig 2. Flow chart of the present study. HBO, hyperbaric oxygen therapy.

Time to pain relief in the 60 patients who presented with pain at inclusion was similar in the two treatment arms (HR = 1.00; 95% CI, 0.52 to 1.89; $P = .99$).

Finally, two patients died in each treatment arm ($P = .99$). One patient died suddenly from a carotid rupture, another from nosocomial pneumonia, and two patients died from cancer relapse.

Adverse Events and Observance

The observance of treatment was similar in both arms. All patients received the treatment to which they were assigned. The mean arterial oxygen tension was 1,850 ± 125 mmHg (mean ± standard deviation) in the HBO arm and 119 ± 25 mmHg in the placebo arm.

There were few complications of hyperbaric sessions in the placebo arm (Table 2). One patient in the placebo arm had seizures during hyperbaric session. As his arterial oxygen tension was only 95 mmHg, oxygen toxicity was ruled out. During follow-up, seizures were found to be related to brain metastasis of a lung cancer.

DISCUSSION

This randomized, sequential, double-blind, placebo-controlled trial failed to show any beneficial effect of HBO in patients with overt mandibular radionecrosis. Decision to stop the trial was based on a sequential procedure that showed no evidence for the superiority of HBO over the placebo. In addition, HBO failed to slow the progression of the disease and to accelerate pain relief.

More severe forms of radionecrosis, characterized by mandibular fracture or bony reabsorption to the inferior border of the mandible, were not included for three main reasons. Firstly, there was no consensus among the 12 participating academic centers to standardize surgical procedures for mandibular resection and microvascular reconstruction. Secondly, almost one third of the investigators were reluctant to include severely ill patients in a placebo-controlled trial. Finally, we were expecting that HBO would prevent progression to fracture and avoid mandibular

Table 1. Main Baseline Characteristics According to Randomization Group

	Experimental Group (n = 31)		Control Group (n = 37)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	53		55	
First and third quartiles	47-61		49-62	
Sex, male	25	80.7	34	91.9
Tobacco	26	83.9	33	89.2
Hypertension	4	12.9	6	16.2
Diabetes	3	9.7	2	5.4
Diffuse arteritis	3	9.7	2	5.4
Chronic alcoholism	16	51.6	23	62.2
Past history of cancer				
Time elapsed since diagnosis, months				
Median	48		34	
First and third quartiles	21-85		18-71	
Tumoral site(s)*				
Floor of mouth	11	35.5	15	40.5
Tongue	13	41.9	11	29.7
Tonsil	5	16.1	5	13.5
Soft palate	6	19.3	9	24.3
Solid palate	1	3.2	3	8.1
Lips	1	3.2	0	0
Buccal mucosa	7	22.6	4	10.8
Radiotherapy				
Iridium implant	7	22.6	11	29.7
External beam	27	87.1	30	81.1
Duration of irradiation, days				
Median	58		61	
First and third quartiles	41-63		55-71	
Total dose, Gy				
Median	70		70	
First and third quartiles	65-70		60-75	
Chemotherapy	14	45.2	13	35.1
Surgery	20	64.5	22	61.1
General Status				
Karnofsky index				
Median	100		90	
First and third quartiles	90-100		80-100	
Albumin level, g/L				
Median	40		42	
First and third quartiles	37-41		38.5-45.5	
History of radionecrosis				
Group A	25	80.7	29	78.4
Time elapsed since optimal conservative treatment, months				
Median	2		4	
First and third quartiles	1-8.5		1.5-8.5	
Cause of necrosis				
Spontaneous	15	48.4	18	48.7
Infection	5	16.1	6	16.2
Surgery	0	0	0	0
Dental extraction prior to radiation	1	3.2	3	8.1
Dental extraction after radiation	11	35.5	11	29.7
Trauma	0	0	1	2.7
Other	1	3.2	0	0
Clinical sign(s)*				
Pain	27	87.1	33	89.2
Anesthesia in the distribution of the inferior alveolar nerve	3	9.7	3	8.1
Trismus	13	41.9	16	43.2
Area of exposed bone	15	48.4	23	62.2
Diameter of the main area of exposed bone, mm				
Median	13.5		18	
First and third quartiles	10-20		12.5-20.0	

(continued on following page)

Table 1. Main Baseline Characteristics of the 68 Patients According to Randomization Group (continued)

	Experimental Group (n = 31)		Control Group (n = 37)	
	No. of Patients	%	No. of Patients	%
Site of necrosis*				
Symphysis	2	7	4	13
Body	22	78	25	81
Angle	8	28	3	10
Ramus	3	11	1	3
Number of bone sequestra				
Median	1		1	
First and third quartiles	1-1		1-2	
Previous surgical cure	5	16.1	7	18.9

*Possibly more than one.

resection in mild to moderate radionecrosis. Therefore, the findings of this study may not be extrapolated to the more severe forms of mandibular radionecrosis.

The definition of recovery was based on explicit criteria that were blindly recorded in all patients by the same surgeon. As the study focused on the mild to moderate form of osteoradionecrosis, we considered as failures of the therapeutic strategy the progression from group A (stage I of Marx's classification) to group B (stage II of Marx's classification), that is, the need for the patient to be operated on, and the need for mandibular resection for patients in group B. Thus, this restrictive definition of recovery from osteoradionecrosis explained the observed low rate of treatment success in both arms. Nevertheless, in the placebo arm, the observed recovery rate was higher than previously reported in non–HBO-treated patients.[5,12] The recovery rate achieved with HBO alone was 19.3%, reaching 85% after one or two surgical procedures, in keeping with results obtained in previous uncontrolled studies.[1,8,12,17]

The therapeutic protocol of 30 preoperative HBO sessions at 2.4 ATA for 90 minutes each, followed by 10 treatments after surgery, was in keeping with current recommendations at the time the study was designed.[9] The hyperbaric sessions were delivered twice daily in order to shorten the overall treatment duration. Whether a more prolonged HBO treatment (ie, more than 30 + 10 dives) would have resulted in different findings requires additional investigations. However, previous studies showed that the maximum angiogenesis occurred around 20 HBO exposures.[7,18] Recent data suggested that induction of angiogenic cytokines during wound healing may result from other mechanisms than hypoxia,[19] such as lactate tissue levels.[20] Then, it seems very unlikely that two hyperbaric sessions per day have resulted in suppression of

Table 2. Main Treatment Features (first period) According to Randomization Group (N = 68)

	Experimental Group (n = 31)		Control Group (n = 37)		
	No. of Patients	%	No. of Patients	%	*P*
No. of performed sessions					.65
Median	25		26		
First and third quartiles	22-27		22-29		
No. of discontinued sessions per patient due to complications					.13
0	29	93.6	32	86.5	
1	0	0	4	10.8	
2	2	6.4	1	2.7	
Number of sessions with complication per patient					
0	30	96.8	28	75.7	.011
1	0	0	7	18.9*	
2	1	3.2†	2	5.4†	

*Complications included otic barotraumas in four patients, seizure in one patient and technical problems in two patients.
†Complications were otic barotraumas.

macrophage-derived angiogenic factors. Moreover, in a recent animal study, HBO delivered twice daily for 7 days following wounding was associated with a significant increase in vascular endothelial growth factor, though wound oxygen increased from nearly 0 mmHg up to 600 mmHg.[21] This increase in the angiogenic factor lasted up to 3 days after cessation of HBO.

Patients in the placebo arm were breathing (at 2.4 ATA) a gas containing 9% oxygen, which is equivalent to breathing 21% oxygen at surface pressure. A similar placebo has been recently used to evaluate HBO for radiation-induced brachial plexopathy.[22] We found no previous data suggesting that pressure itself or high concentration of nitrogen may impact the healing process.

Numerous uncontrolled trials reported recovery rates of 15% to 45% with HBO alone, and of 20% to 90% with HBO combined with surgery.[1,8,12,17] The only previously published randomized trials had enrolled 12 patients with overt radionecrosis, and had concluded that a 2-hour HBO session at 2.0 ATA 5 days a week for 8 weeks significantly improved outcomes of these patients when compared to a 2-hour HBO session at 1.2 ATA.[11] This study was unblinded, and the authors did not report data on which one can evaluate the reliability of their conclusions. Therefore, we could not analyze the reasons for the discrepancies in findings from the two studies. However, one can speculate that substantial advances in conservative treatments, including antibiotics and surgical procedures since 1979, may have accounted for better recovery rates in the placebo-treated patients observed in our study. On the other hand, the observed lack of significant difference between HBO and placebo agreed with previous reports in animals[23] and humans[24] that failed to demonstrate increased irradiated bone-healing capacity with HBO. Moreover, the observed comparable transcutaneous oxygen saturation between irradiated and nonirradiated skin challenged the concept that ischemia is the primary mechanism for radionecrosis,[25] favoring the fibro-atrophic mechanisms.[4] Finally, our results are also in keeping with those of a recent double-blind, randomized trial showing no evidence to support a 30 HBO exposures treatment for radiation-induced brachial plexopathy.[22]

Thus, HBO should not be recommended to treat patients with overt mandibular radionecrosis and no evidence for fracture or bony reabsorption to the inferior border. Further studies are needed to assess the efficacy and safety of HBO in these more severe forms of mandibular radionecrosis.

Appendix

Study organization: *Steering committee:* D. Annane, S. Chevret (statistician), J. Depondt, P. Gajdos (chair), P. Géhanno.

Independent Efficacy and Safety Monitoring Board: Professor Bollaert (Hyperbaric Center, CHU Hôpital Central), Dr Bretel (Clinique Charlebourg—Institut Gustave Roussy), Dr Fabre (Service ORL, Hôpital Max Fouretier).

Pharmacist: Maryvonne Villart.

Monitor: Caroline Fisch, Délégation à la Recherche Clinique, Hôpital Saint Louis, Paris.

Research Assistant: Nathalie Zinsou, Délégation à la Recherche Clinique, Hôpital Saint Louis, Paris.

Hyperbaric chamber staff: Jean Claude Raphael, MD, Bernard Clair, MD; Nurses Michèle Colas, Martin De Mecquenem, Christian Dedieu, Christian Dubois, Christian Fernandez, Michel Lebescont, Florence Michon, Josiane Panariello, Michel Roustan, Pascal Wawrzyniak, Aziz Rhidane, Céline Burkhardt.

Participating investigators and centers (ORN96 study group): Didier Boucarra (Service d'ORL) and Jean-Pierre Lezy (Service de Stomatologie), Hôpital Beaujon, Clichy; Frédéric Chabolle and Isabelle Wagner (Service d'ORL), C.M.C. Foch, Suresnes; Didier Maurice (Service d'Odontologie), Hôpital Hotel Dieu, Paris; Vlado Smatt (Service de Stomatologie et Chirurgie Maxillofaciale), Centre René Huguenin, Saint Cloud; Patrice Tran Ba Huy (Service d'ORL), Hôpital Lariboisiere, Paris; Catherine Hannaire and Mohamed Maza (Service de Stomatologie), Hôpital Henri Mondor, Creteil; Estelle Favre-D'Auvergne (Service de Stomatologie), Hôpital Pitie Salpetriere, Paris; Michel Ouayoun (Service d'ORL Chirurgie Cervicofaciale), Hôpital Saint Antoine, Paris; Jean Paul Monteil (Service d'ORL), Hôpital Saint Louis, Paris; Jean Lacau Saint-Guily (Service d'ORL), Hôpital Tenon, Paris; Guy Renou (Service d'ORL), CHI Léon Touhladjian, Poissy, France.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Hart GB, Strauss MB. Hyperbaric oxygen in the management of radiation injury, In Schmutz J (ed): Stiftüng für Hyperbaric Medizin. Basel, Proceedings 1st Swiss Symposium on Hyperbaric Medicine, 1986, pp 31-51
2. Balogh JM, Sutherland SE: Osteoradionecrosis of the mandible: A review. J Otolaryngol 18:245-250, 1989
3. Amodeo N: Reaction and necrotic changes following radium therapy in cancer of the mouth. Am J Cancer 23:600-604, 1936
4. Delanian S, Lefaix JL: Mature bone radionecrosis: From recent physiopathological knowledge to an innovative therapeutic action. Cancer Radiother 6:1-9, 2002
5. Marx RE, Ames JR: The use of hyperbaric oxygen as an adjunct in the treatment of osteoradionecrosis of the mandible. J Oral Maxillofac Surg 40:412-418, 1982
6. Kulonen E, Silver IA: Local and systemic factors which affect the proliferation of fibroblasts, In Kulonen E (ed): Biology of the Fibroblast. London, England, Academic Press, 1973, pp 521-523
7. Marx RE, Ehler IA, Tayapongsak P, et al: Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg 160:519-524, 1990
8. Marx RE, Johnson RP. Problem wounds in oral and maxillofacial surgery: The role of

hyperbaric oxygen, In Davis JC, Hunt TK (eds): Problem wounds: The role of oxygen. New York, Elsevier, 1988, pp 65-123

9. Tibbles PM, Edelsberg JS: Hyperbaric oxygen therapy. N Engl J Med 334:1642-1648, 1996

10. Marx RE, Johnson RP, Kline SN: Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dent Assoc 111:49-54, 1985

11. Tobey RE, Kelly JF: Osteoradionecrosis of the jaws. Otolaryngol Clin North Am 12:183-186, 1979

12. Mansfield MJ, Sanders DW, Heimback RD, et al: Hyperbaric oxygen as an adjunct in the treatment of osteoradionecrosis of the mandible. J Oral Surg 39:585-589, 1981

13. Whitehead J: The design and analysis of sequential clinical trials (2nd ed). New York, Ellis Horwood, 1992

14. Kaplan E, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

15. Peto R, Peto J: Asymptotically efficient rank invariant test procedures (with discussion). J R Stat Soc A 135:185-206, 1972

16. Cox DR; Regression models and life tables (with discussion). J R Stat Soc B 34:187-220, 1972

17. David LA, Sandor GKB, Evans AW, et al: Hyperbaric oxygen therapy and mandibular osteoradionecrosis: A retrospective study and analysis of treatment outcomes. J Can Dent Assoc 67:384-392, 2001

18. Store G, Granström G: A morphologic and morphometric study of mandibular osteoradionecrosis. Proceedings of the XXI European Underwater and Baromedical Society:105-110, 1995

19. Haroon ZA, Raleigh JA, Greenberg CS, et al: Early wound healing exhibits cytokine surge without evidence of hypoxia. Ann Surg 231:137-147, 2000

20. Constant JS, Feng JJ, Zabel DD, et al: Lactate elicits vascular endothelial growth factor from macrophages: A possible alternative to hypoxia. Wound Repair Regen 8:353-360, 2000

21. Sheikh AY, Gibson JJ, Rollins MD, et al: Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. Arch Surg 135:1293-1297, 2000

22. Pritchard J, Anand P, Broome J, et al: Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. Radiother Oncol 58:279-286, 2001

23. Johnsson AA, Jacobsson M, Granstrom G, et al: A microradiographic investigation of cancellous bone healing after irradiation and hyperbaric oxygenation: A rabbit study. Int J Radiat Oncol Biol Phys 48:555-563, 2000

24. Maier A, Gaggl A, Klemen H, et al: Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. Br J Oral Maxillofac Surg 38:173-176, 2000

25. Rudolph R, Tripuraneni P, Koziol JA, et al: Normal transcutaneous oxygen pressure in skin after radiation therapy for cancer. Cancer 74: 3063-3070, 1994