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Clinical Investigation

HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery

Richard J. Shaw, FRCS,[*] Christopher J. Butterworth, FDSRCS,[†] Paul Silcocks, FRCPath,[‡] Binyam T. Tesfaye, BSc,[§] Matthew Bickerstaff, BA,[‡] Richard Jackson, PhD,[‡] Anastios Kanatas, FRCS,[‖] Peter Nixon, FDS,[¶] James McCaul, FRCS,[#] Prav Praveen, FRCS,[**] Terry Lowe, FRCS,[††] Manuel Blanco-Guzman, FRCSI,[‡‡] Lone Forner, PhD,[§§] Peter Brennan, FRCS,[‖‖] Mike Fardy, FRCS,[¶¶] Richard Parkin, FRCS,[##] Gary Smerdon, PhD,[***] Ruth Stephenson, FRCA,[†††] Tristan Cope, FRCA,[‡‡‡] and Mark Glover, MFOM[§§§]

***University of Liverpool, Liverpool, United Kingdom; [†]Maxillofacial Prosthodontics, Department of Maxillofacial Surgery, University Hospital Aintree, Liverpool, United Kingdom; [‡]Cancer Research UK Liverpool Clinical Trials Unit, University of Liverpool, Liverpool, United Kingdom; [§]Cancer Research UK Liverpool Cancer Trials Unit, Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom; [‖]OMFS Department, Leeds Dental Institute, Leeds, United Kingdom; [¶]Restorative Department, Leeds Dental Institute, Leeds, United Kingdom; [#]Regional Maxillofacial Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom; [**]Maxillofacial Office, Queen Elizabeth Hospital, Birmingham, United Kingdom; [††]Aberdeen Royal Infirmary, Aberdeen, Scotland; [‡‡]Maxillofacial Unit, Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust, Taunton, United Kingdom; [§§]Departments of Anesthesia and Oral and Maxillofacial Surgery, Centre of Head and Orthopedics, Copenhagen University Hospital, Copenhagen, Denmark; [‖‖]Maxillofacial Unit, Queen Alexandra Hospital, Portsmouth, United Kingdom; [¶¶]University Hospital of Wales, Cardiff, Wales, United Kingdom; [##]OMFS Department, ABUHB, Newport, Wales, United Kingdom; [***]DDRC Healthcare, Hyperbaric Medical Centre,*

Reprint requests to: Richard J. Shaw, MD, FDS, FRCS, Professor of Head and Neck Surgery, Department of Molecular and Clinical Cancer Medicine, North West Cancer Research Centre, The University of Liverpool Cancer Research Centre, Roy Castle Building, 200 London Road, Liverpool, L3 9TA, United Kingdom. Tel: 0151 794 8832; E-mail: rjshaw@liv.ac.uk

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Plymouth, United Kingdom; [†††]*NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, Scotland;*
[‡‡‡]*North West Recompression Unit, Murrayfield Hospital, Holmwood, United Kingdom; and*
[§§§]*Hyperbaric Medicine Unit, St. Richard's Hospital, Chichester, United Kingdom*

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Summary

The results of this multicenter, randomized, controlled trial refute earlier positive results for hyperbaric oxygen therapy in the prevention of mandibular osteoradionecrosis. Both study arms had a very low rate of osteoradionecrosis (6% overall). This is only the second randomized trial in this setting and the only one in the era of modern radiation therapy techniques. Our results suggest that the continued widespread prescription of hyperbaric oxygen therapy in prevention of mandibular osteoradionecrosis is not justified.

Purpose: Hyperbaric oxygen (HBO) has been advocated in the prevention and treatment of osteoradionecrosis (ORN) of the jaw after head and neck radiation therapy, but supporting evidence is weak. The aim of this randomized trial was to establish the benefit of HBO in the prevention of ORN after high-risk surgical procedures to the irradiated mandible.

Methods and Materials: HOPON was a randomized, controlled, phase 3 trial. Participants who required dental extractions or implant placement in the mandible with prior radiation therapy >50 Gy were recruited. Eligible patients were randomly assigned 1:1 to receive or not receive HBO. All patients received chlorhexidine mouthwash and antibiotics. For patients in the HBO arm, oxygen was administered in 30 daily dives at 100% oxygen to a pressure of 2.4 atmospheres absolute for 80 to 90 minutes. The primary outcome measure was the diagnosis of ORN 6 months after surgery, as determined by a blinded central review of clinical photographs and radiographs. The secondary endpoints included grade of ORN, ORN at other time points, acute symptoms, pain, and quality of life.

Results: A total of 144 patients were randomized, and data from 100 patients were analyzed for the primary endpoint. The incidence of ORN at 6 months was 6.4% and 5.7% for the HBO and control groups, respectively (odds ratio, 1.13; 95% confidence interval, 0.14-8.92; $P = 1$). Patients in the hyperbaric arm had fewer acute symptoms but no significant differences in late pain or quality of life. Dropout was higher in the HBO arm, but the baseline characteristics of the groups that completed the trial were comparable between the 2 arms.

Conclusions: The low incidence of ORN makes recommending HBO for dental extractions or implant placement in the irradiated mandible unnecessary. These findings are in contrast with a recently published Cochrane review and previous trials reporting rates of ORN (non-HBO) of 14% to 30% and challenge a long-established standard of care.

Introduction

Osteoradionecrosis (ORN) is exposed necrotic bone after radiation therapy in the absence of cancer recurrence.[1,2] Mandibular ORN is a common complication of head and neck radiation therapy causing pain, infection, and malnutrition. The incidence of head and neck malignancy and use of radiation therapy is increasing,[3] as is survival[4]; thus, the population at risk for ORN is increasing.

The risk of ORN is higher in the posterior mandible and if >60 Gy has been received.[5,6] To prevent ORN, dental health is optimized before radiation therapy[7]; however, dental surgery, such as extractions or implant placement, is often indicated. The risk of such procedures in precipitating ORN is unknown but has been reported as 20% to 30%.[6,8] The overall cumulative incidence of spontaneous ORN may have been reduced with the adoption of intensity modulated radiation therapy,[9,10] but the specific risk for patients as a result of dental procedures is less clear.

The role of hyperbaric oxygen (HBO) in the prevention of mandibular ORN after dental procedures remains controversial.[11,12] Marx's randomized controlled trial[8] showed a lower incidence of ORN after dental extractions with HBO (5.4%) than with penicillin (29.9%). Vudiniabola et al[13] showed that 1 of 29 patients who received HBO (3.4%) developed ORN, and 1 of 7 patients who did not receive HBO (14.3%) developed ORN. Prophylactic HBO became a standard of care for high-risk dental extractions[14] on the basis of this limited evidence. Other trials have not demonstrated a benefit for HBO in the treatment of established mandibular ORN[15] or in late radiation toxicities to other anatomic sites.[16] Similarly, controversy surrounds the role of HBO in the placement of implants in the irradiated mandible, with conflicting evidence[17,18] from retrospective series. The costs and logistic arrangements implicit in 30 daily treatments with HBO present a barrier to universal adoption. A recent Cochrane review[19] concluded that HBO reduced the chance of ORN after a tooth extraction but stressed the need for further well-designed studies.

To address the paucity of evidence, we conducted the HOPON trial. The aim of this randomized trial was to establish the benefit of HBO in the prevention of ORN after high-risk surgical procedures to the irradiated mandible. Additionally, the HOPON trial aimed to define the changes in acute symptoms accompanying surgery, long-term pain, and quality of life (QoL), resulting from the use of HBO and to determine the risk of ORN.

Methods and Materials

The HOPON trial was a randomized, controlled, phase 3 study. The patients and site investigators were unblinded, but assessment of the primary endpoint was blinded and remotely assessed by a blinded expert panel of investigators. The trial was conducted in 16 acute UK hospitals, 1 acute hospital in Denmark, and 9 UK hyperbaric medicine facilities registered with the British Hyperbaric Association. The HOPON trial protocol was granted ethical approval by the Greater Manchester Central Research Ethics Committee (REC reference 08/H1008/32). The study protocol is available at https://www.lctu.org.uk/HOPONProtocol, and a more detailed description has been published previously.[20] The phase 3 analysis incorporates data from the preceding HOPON phase 2 feasibility study with parallel trial inclusion, randomization, procedures, and assessments for the first 48 randomized patients.

Participants

Eligible participants were men and women aged $\geq$18 years with an indication for surgery to the mandible and prior radiation therapy to the mandible of at least 50 Gy. Indications for surgery included extraction of premolar or molar teeth or the placement of osseointegrated dental implants.

Randomization

Eligible patients were randomly assigned (1:1) to receive or not receive HBO. Allocation of treatment was unblinded to site investigators and patients.

Procedures

Patients in both arms of the trial were given chlorhexidine mouthwash and antibiotics. Pre- and postoperative chlorhexidine mouthwash 0.2% was used in a volume of 10 mL, rinsed around the mouth for approximately 1 minute and spat out, 3 times daily for 5 days postoperatively. Orally administered antibiotics comprised amoxicillin 3 g 1 hour preoperatively, or 1 g administered intravenously, and 250 mg 3 times daily for 5 days postoperatively. Suitable alternatives were used to substitute for chlorohexidine or amoxicillin in cases of allergy.

For patients in the HBO arm, oxygen was administered at 2.4 atmospheres absolute for 80 to 90 minutes in 30 daily treatments (20 immediately before and 10 after surgery). The trial procedures are summarized in Figure 1. For patients who developed ORN, subsequent management was not specified in the trial protocol; however, the grade of ORN was followed to the 12-month time point.

Outcomes

The primary outcome measure was the presence or absence of ORN 6 months after surgery, determined by a blinded central review of clinical photographs and radiographs and classified using the modified Notani score (Table E1; available online at https://doi.org/10.1016/j.ijrobp.2019.02.044).[1,20,21] The secondary endpoints were ORN similarly assessed at 3 and 12 months, pain, and QoL. Additionally, acute symptoms (pain, swelling, trismus, and diet) were self-recorded during the first week after surgery.

Sample size: stopping rules

The incidence of ORN in the control arm was anticipated to be 18% to 19% on the basis of prior trials, such as those by Marx et al[8] and Vudiniabola et al[13] who reported comparable rates of 30% and 14%, respectively. Accordingly, 103 evaluable patients per group would provide 80% power to detect an odds ratio (OR) of 0.23, which equates to a rate of 18.5% in the control arm and 5% in the HBO treatment arm, with a difference of 13.5%. Estimating the dropout rate at 7%, recruitment was planned for 221 patients. A single interim analysis was planned when 100 patients had been followed up for 6 months, using the Peto stopping rule for the primary efficacy outcome.

Statistical analysis

For patients in the HBO arm, the additional treatment before surgery increased the risk for drop out compared with the standard arm. Therefore, the full analysis set used for the primary analyses was defined as all randomized patients who received surgery according to the treatment group originally allocated. The validity of this approach was supported by a range of sensitivity analyses. The primary test of efficacy was performed using a Fisher's exact test with exact logistic regression to obtain exact 95% confidence intervals (CIs) about an OR. The null hypothesis was that HBO treatment was not more effective than standard care (ie, the OR was not statistically different from 1), and the alternate hypothesis was that HBO treatment was superior with an OR $\leq$0.23. A 2-sided test with a P-value $<$.05 was declared statistically significant. The

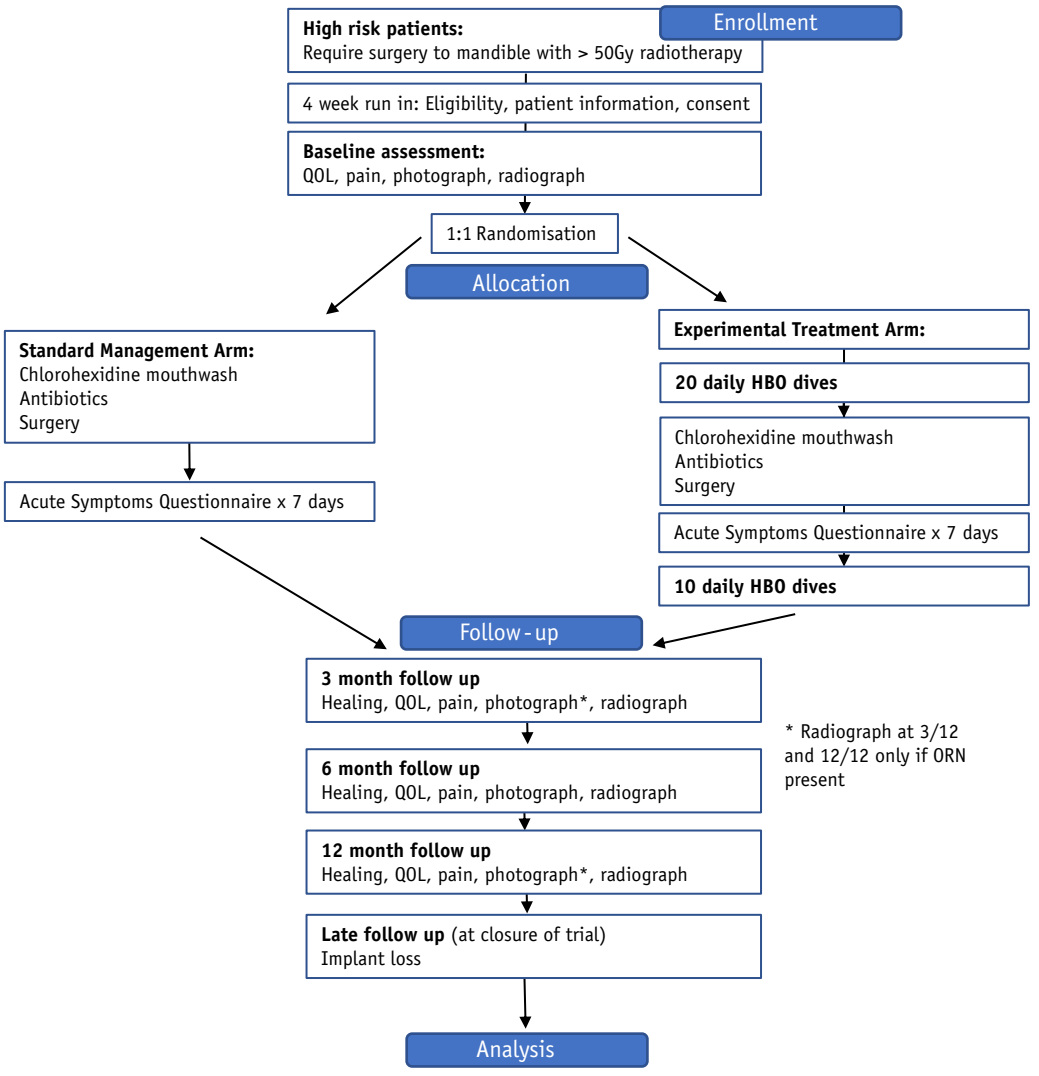

Fig. 1. HOPON trial schema.

significance tests for the secondary endpoints were 2-sided at 5%, accompanied by 95% 2-sided CIs.

An independent safety data monitoring committee oversaw the HOPON trial.

Results

A total of 144 patients were randomized between 2008 and 2016, with 72 patients (50%) in the HBO arm and 72 (50%) in the non-HBO arm. Dropout after randomization but before treatment was higher in the HBO arm, at 17 of 72 patients (24%) compared with 6 of 72 patients (8%) in the non-HBO arm. Nineteen patients (13%) withdrew from the study between surgery and the primary endpoint (7 of 72 patients [10%] in the HBO arm and 12 of 72 patients [17%] in the non-HBO arm). One patient in each arm was determined to be ineligible on review, and a total of 100 patients were available for the primary analysis: 47 in the HBO arm and 53 in the non-HBO arm (Fig. 2). An additional 7 patients (4 in the HBO group and 3 in the non-HBO group) withdrew from the study after providing data on the primary outcome. Despite the differences in dropout rate, the baseline characteristics were similar whether the comparison was made on patients randomized, per protocol, or those analyzed for the primary endpoint (Table 1).

The overall incidence of ORN at the primary endpoint was 6 of 100 patients (6%): 3 of 47 patients (6.4%) in the HBO arm and 3 of 53 patients (5.7%) in the non-HBO arm. The OR for ORN was 1.13 with a 2-sided Fisher's exact test $P > .99$ (95% CI, 0.14-8.92). For patients undergoing dental extractions, the OR was 0.72, with a 2-sided Fisher's exact $P > .99$ (95% CI, 0.06-6.66). The unblinded site investigators' assessment of ORN at 6 months also showed no difference (OR, 1.02; 2-sided Fisher's exact $P > .99$; 95% CI, 0.31-3.27). The independent data monitoring

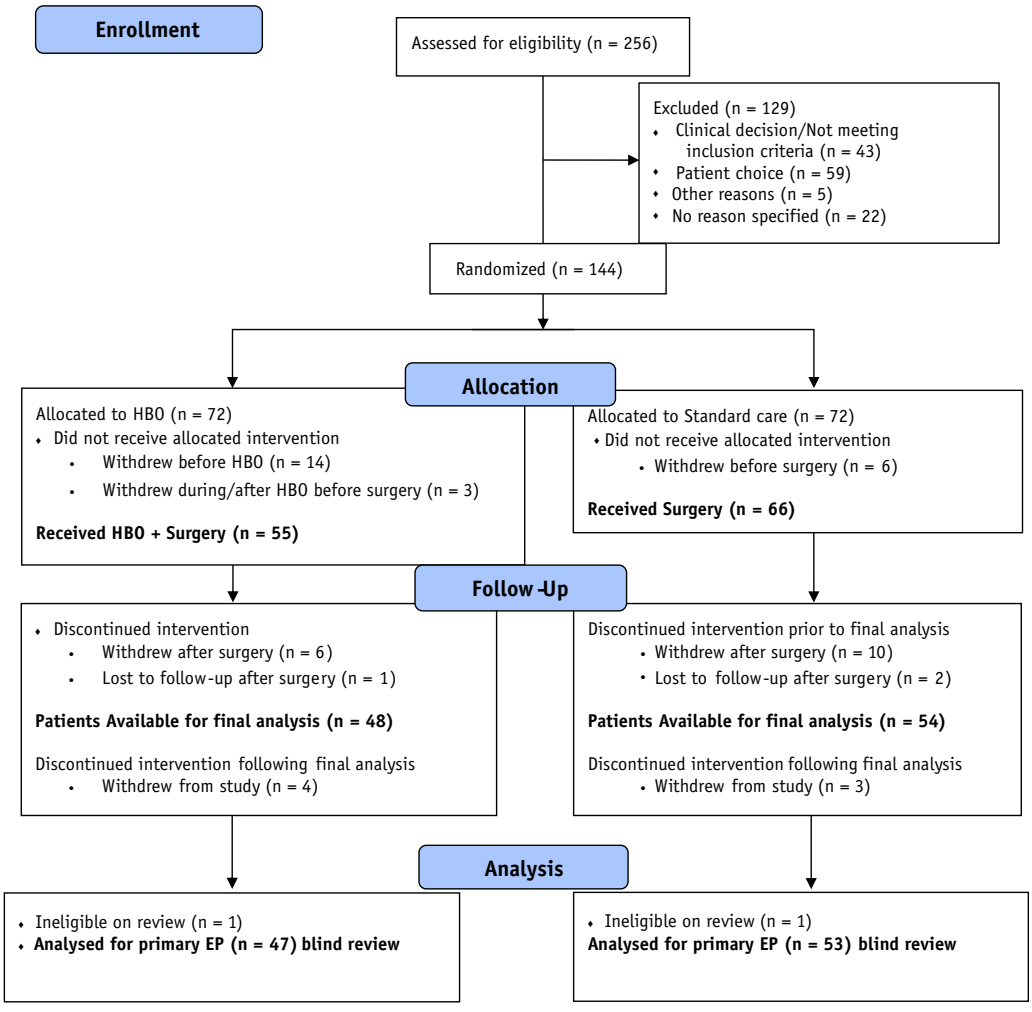

Fig. 2. Trial consort diagram.

Table 1 Baseline characteristics of patients analyzed per protocol (ie, completed allocated hyperbaric oxygen treatment, received surgery, and followed until 6-month primary endpoint assessment)

Characteristic (reviewed patients)	Hyperbaric oxygen arm (n = 47)	Control arm (n = 53)	Total (N = 100)
Age, mean (standard deviation), y	58.3 (10)	58.2 (10.4)	58.2 (10.1)
Men, n (%)	14 (30)	14 (27)	28 (28)
Smoking status, n (%)			
Never	14 (29)	17 (32)	31 (31)
Past	23 (48)	26 (49)	49 (49)
Current	10 (21)	10 (18)	20 (20)
Missing	0 (0)	0 (0)	0 (0)
Alcohol consumption, n (%)			
Never	4 (12)	3 (7)	7 (10)
Past	5 (15)	10 (25)	15 (21)
Current	24 (72)	26 (66)	50 (69)
Missing	14 (42)	14 (35)	28 (28)
Radiation therapy			
Radiation therapy dose, mean (standard deviation), Gy	62.8 (7.8)	63 (10.2)	62.9 (9.1)
Radiation therapy duration, mean (standard deviation), wk	6.1 (1.6)	6.2 (1.7)	6.2 (1.7)

committee recommended closing the trial after 100 evaluable patients because the rate of ORN was much less than that assumed, precluding statistically significant efficacy analyses for HBO.

The incidence of ORN at 3 months was 7%, with 3 of 45 patients (7%) in the HBO arm and 4 of 55 patients (7%) in the non-HBO arm (OR, 0.91; 2-sided Fisher's exact test $P > .99$; CI, 0.13-5.72). No patients with ORN at the 6-month primary endpoint had healed by 12 months, with the exception of 1 patient who was lost to follow-up between these time points. No new cases of ORN developed between 6 and 12 months. The grade of ORN at 6 months was Notani grade 1 for 2 patients, Notani grade 2 for 1 patient, and Notani grade 3 for 3 patients. Of the 100 patients available for analysis, 16 (16%) had no dental extraction with a single case of ORN (6%), and 17 patients had a single extraction during surgery; 2 of these patients had ORN (11%). Sixty-seven patients (67%) had multiple extractions, with 3 (4%) of these patients experiencing ORN. The difference in ORN between extraction status was not statistically significant ($P = .558$).

The incidence of minor bone spicules (MBS) at the primary endpoint was 13%: 5 of 47 patients (10%) in the HBO arm and 8 of 53 (15%) in the non-HBO arm (OR, 0.67; 2-sided Fisher's exact test $P = .5642$; 95% CI, 0.16-2.55). MBS was managed entirely conservatively without sequestrectomy, and because all cases with MBS in the primary analysis had fully healed by 12 months, it is concluded this was by natural exfoliation.

Analysis of the acute symptoms questionnaire showed that, for the area under the curve, patients had less severe symptoms in the first 7 days after surgery in the HBO arm for pain ($P = .0458$), swelling ($P = .0182$), bleeding ($P = .0375$), mouth opening ($P = .004$), and eating ($P = .004$; Table 2). The patient data were unblinded with regard to allocation, and these results reflect an analysis of the 75% of questionnaires that were returned (39 patients in the HBO arm, 36 patients in the non-HBO arm). A higher proportion (65%) of patients in the HBO arm were comfortable at day 8 after surgery compared with patients in the non-HBO arm (35%; exact OR, 2.79; 2-sided Fisher's exact test $P = .038$; 95% CI, 1.01-8.05).

Patients' experience of pain as assessed by visual analogue scores collected at baseline and at 3, 6, and 12 months are summarized in Table 3. Pain scores were lower in the HBO arm than in the non-HBO arm at all time points. However, the differences were small and of borderline statistical significance, and the absolute levels of pain were very low at 3, 6, and 12 months. Pain scores reduced by 0.044 units per month in the non-HBO arm and 0.076 units in the HBO arm. These very small differences (ie, <0.1 in the context of a 0-10 scale) are of dubious clinical significance (Table E2; available online at https://doi.org/10.1016/j.ijrobp.2019.02.044).

The measures of QoL in each arm were similar, with a marginal advantage for the HBO arm, which is partly attributable to a slight advantage at baseline. QoL data are presented as a summary of trend for composite physical score (Fig. 3) and composite social score (Fig. 4) for the University of Washington QoL data obtained at baseline and at 3, 6, and 12 months. The changes in University of Washington QoL data seen over the trial time points were modest and did not differ significantly between the HBO and non-HBO arms.

Pain scores were very low, both for patients with full healing (0.1; standard deviation [SD], 0.23; 81 patients) and those with MBS (0.1; SD, 0.22; 11 patients). In contrast, mean pain score was higher at 0.3 (SD, 0.3; 6 patients) for patients with Notani grade 1, 2, or 3 ORN. These data show that the symptoms of patients with MBS were more similar to those of healed patients than those with ORN. The categorization of MBS with other healed patients appears to be justified.

For patients who received dental implants, the loss of any implant was recorded beyond 12 months until the date of trial closure. Implant survival after surgery was high, at 95% at 24 months (95% CI, 74%-99%) and 83% at 48 months (95% CI, 48%-95%). There were 13 implant failures among 4 patients, with 4 implants being lost in 1 patient in the HBO arm and 9 implants in 3 patients in the non-HBO arm. The hazard ratio for implant loss in the HBO versus non-HBO arm was 1.39 (95% CI, 0.16-12.09; $P = .765$; adjusted for clustering by patient).

Safety within the trial was good, and adverse events related to HBO tended to be of low grade. There were no significant differences in death, hospital admission, incapacitation, or further surgery between the 2 arms. Adverse events potentially attributable to HBO are shown in Table E3 (available online at https://doi.org/10.1016/j.ijrobp.2019.02.044). Serious adverse events were mostly related to subsequent malignancies, occurring in 13% of patients within 12 months. Recurrence of head and neck malignancy occurred in 4%, at a new site in 6%, and of uncertain origin in 3%. There were no significant differences in the incidence of malignancy between the arms, with 7 diagnoses in 47 patients (15%) in the HBO arm versus 6 in 53 patients (11%) in the non-HBO arm.

A range of sensitivity analyses was performed to explore any potential effect of dropout on the primary endpoint (Table E4; available online at https://doi.org/10.1016/j.ijrobp.2019.02.044). None provided any conclusive support for either benefit or harm, which shows that the overall results of the study are robust under a variety of assumptions.

Discussion

The incidence of ORN in the HOPON trial was 6%; therefore, the risk to irradiated patients who need dental procedures is too low to routinely justify the use of HBO and likely precludes future prevention trials in this setting. This finding is in itself highly significant, contradicting the

Table 2 Acute symptoms questionnaire by trial arm

Postsurgery day	HBO pain	Standard pain	HBO swelling	Standard swelling	HBO bleeding
1	2.55 (SD = 1.17; N = 42)	2.92 (SD = 1.09; N = 37)	2.25 (SD = 1.03; N = 40)	2.65 (SD = 1.18; N = 37)	1.83 (SD = 0.97; N = 41)
2	2.19 (SD = 1.06; N = 42)	2.7 (SD = 1.13; N = 37)	2.07 (SD = 0.96; N = 41)	2.59 (SD = 1.17; N = 37)	1.32 (SD = 0.57; N = 41)
3	2.12 (SD = 1.09; N = 42)	2.43 (SD = 1.07; N = 37)	1.83 (SD = 0.8; N = 41)	2.38 (SD = 0.92; N = 37)	1.12 (SD = 0.4; N = 41)
4	1.83 (SD = 0.93; N = 42)	2.16 (SD = 0.99; N = 37)	1.66 (SD = 0.76; N = 41)	1.95 (SD = 0.97; N = 37)	1.12 (SD = 0.4; N = 41)
5	1.78 (SD = 1.08; N = 41)	2.16 (SD = 1.04; N = 37)	1.43 (SD = 0.64; N = 40)	1.73 (SD = 0.77; N = 37)	1.13 (SD = 0.33; N = 40)
6	1.68 (SD = 1.01; N = 41)	1.92 (SD = 1.06; N = 37)	1.41 (SD = 0.64; N = 39)	1.61 (SD = 0.73; N = 36)	1.05 (SD = 0.22; N = 40)
7	1.59 (SD = .92; N = 41)	1.97 (SD = 1.07; N = 37)	1.31 (SD = 0.47; N = 39)	1.51 (SD = 0.69; N = 37)	1.02 (SD = 0.16; N = 40)
Mean area under the curve	11.53 (SD = 5.55; N = 42)	13.79 (SD = 5.69; N = 37)	9.97 (SD = 3.79; N = 41)	12.36 (SD = 4.74; N = 37)	7.03 (SD = 1.79; N = 41)
P-value		.1625 (.0458)		.0207 (.0182)	

Abbreviations: HBO = hyperbaric oxgen; SD = standard deviation.

Results reflect the analysis of the 75% of returned questionnaires (39 patients in the HBO arm, 36 patients in non-HBO arm). *P*-values are from the joint structural equations model that includes comfort at day 8. Robust standard errors were used because of differences in variance and departures from normality. Univariate Mann-Whitney *P*-values are displayed in brackets.

findings of a recent Cochrane review.[19] These results are in contrast with prior randomized trial evidence,[8] but the overall incidence of ORN in the HOPON trial is consistent with a progressively declining trend reported in retrospective case series,[22] cited as 7% in a recent study.[9] Alternative methods for prophylaxis of ORN include the use of pentoxifylline and tocopherol. The single retrospective series[23] published to date confirms a very low rate of ORN but reinforces the statistical challenges of powering randomized trials.

The low rate of ORN in the present data raises the question of whether subsequent surgery in the irradiated mandible, such as extraction or implant placement, actually causes additional cases of ORN or merely changes the timing of presentation for cases that would have developed spontaneously. The HOPON trial clarifies the incidence and natural progression of ORN in a tightly controlled prospective study, adding significant data to a field dominated by anecdotal and retrospective case series.

The reasons for the apparent reduction in risk of mandibular ORN may be attributable to more stringent dental protocols or more advanced, better targeted radiation therapy techniques, such as intensity modulated radiation therapy.[9,24] Intensity modulated RT can effectively allow salivary glands to be spared with improvements in xerostomia,[10] and it may also have reduced the impact of radiation therapy to the mandible in head and neck malignancy.

With regard to the secondary endpoints, acute symptoms were significantly improved in the week after surgery in patients who received HBO. There was slightly less pain reported by patients in the HBO arm at 3, 6, and 12 months, but these differences were too small to be of clinical relevance. There were only minor and insignificant differences in QoL associated with the use of HBO. As a whole, these symptomatic effects appear to be temporally related to the HBO sessions, decreasing over time. These outcomes reflect unblinded analyses, so the differences may include placebo effect or a biologic mechanism of HBO, which may reflect an anti-inflammatory or anti-infectious effect. Late radiation injury is usually accompanied by vascular atrophy and lacks steep oxygen gradients required for angiogenesis in surgical wounds.[25] This has been reversed in vivo using 30 treatments of HBO, and such mechanisms might be able to improve symptoms in a dental extraction or implant wounds. In a comparable trial of HBO in late radiation tissue injury of the pelvis, the HORTIS trial[26] showed early significant symptomatic benefits associated with HBO, but the subsequent HOT2 trial[16] showed no benefit at 1 year.

The strengths of the HOPON trial are mainly in the robust blinded nature of the primary endpoint assessment and in the comparability between the 2 trial arms. The choice of 6 months as the primary endpoint appears justified because ORN at this time point was stable. No patients with ORN at 6 months had healed by 12 months, and no new cases developed between 6 and 12 months.

The use of the category MBS aided the primary analysis, and its distinction from ORN is of critical importance. Thirteen percent of patients developed MBS at the primary endpoint, which was more than double the incidence of ORN at 6%. The differences between MBS and ORN are clear in terms of severity, extent, symptoms, and progression. All cases of MBS at the 6-month primary endpoint had spontaneously healed without intervention by 12 months, but all cases of ORN at the primary endpoint persisted to 12 months. MBS was essentially asymptomatic, with pain scores comparable to those of patients who had fully healed, but patients with ORN had more pain. The disparity in clinical appearance of ORN versus MBS is illustrated in Figures 5 and 6. Therefore, MBS should be regarded as clinically innocuous and reflects delayed healing rather than progressive bone necrosis. It is concerning that this entity has not been clearly characterized and accounted for in the data of previous trials and series in the field.[1]

The current trial does not address the use of HBO in the management of established ORN with or without surgical resection. Although this has been long established, a previous prospective clinical trial did not find any benefit.[15]

Table 2 Acute symptoms questionnaire by trial arm *(continued)*

Standard bleeding	HBO opening mouth	Standard opening mouth	HBO eating	Standard eating
2.3 (SD = 1.02; N = 37)	1.73 (SD = 0.99; N = 40)	2.58 (SD = 1.32; N = 36)	2.98 (SD = 1.42; N = 40)	4.03 (SD = 1.28; N = 32)
1.7 (SD = 0.81; N = 37)	1.67 (SD = 0.84; N = 39)	2.56 (SD = 1.23; N = 36)	2.5 (SD = 1.4; N = 40)	3.85 (SD = 1.3; N = 33)
1.44 (SD = 0.73; N = 36)	1.48 (SD = 0.75; N = 40)	2.49 (SD = 1.24; N = 37)	2.28 (SD = 1.36; N = 40)	3.68 (SD = 1.42; N = 31)
1.28 (SD = 0.61; N = 36)	1.33 (SD = 0.62; N = 40)	2.16 (SD = 1.19; N = 37)	2.13 (SD = 1.42; N = 40)	3.36 (SD = 1.37; N = 33)
1.3 (SD = 0.62; N = 37)	1.31 (SD = 0.47; N = 39)	2.08 (SD = 1.19; N = 37)	2.08 (SD = 1.35; N = 39)	3.18 (SD = 1.53; N = 33)
1.16 (SD = 0.44; N = 37)	1.28 (SD = 0.46; N = 39)	2 (SD = 1.2; N = 37)	2 (SD = 1.3; N = 39)	3.06 (SD = 1.62; N = 33)
1.31 (SD = 0.86; N = 36)	1.26 (SD = 0.5; N = 39)	1.97 (SD = 1.13; N = 36)	1.9 (SD = 1.29; N = 39)	2.82 (SD = 1.57; N = 33)
8.54 (SD = 3.28; N = 37)	8.44 (SD = 3.51; N = 40)	13.43 (SD = 6.79; N = 37)	13.18 (SD = 7.49; N = 40)	20.42 (SD = 8.14; N = 33)
.0167 (.0375)		.0007 (.0004)		.0002 (.0004)

Another trial in Denmark by the DAHANCA group is underway, exploring the role of HBO with the surgical resection of ORN.

Several difficulties were encountered during the HOPON trial, particularly slow recruitment. In previous work within the portfolio of head and neck cancer trials,[27] we had identified 2 arms of the trial that appeared very different in nature, and many patients would be more likely to express a preference for one arm or the other. Similarly, as HBO has been a long-established standard of care in this setting, it may be that not all recruiting clinicians were able to effectively convey equipoise.[28] The unblinded nature of the data for assessment of acute symptoms, late pain, and QoL means that less weight can be attached to these secondary endpoints than to the primary endpoint. In this regard, the use of sham HBO as a placebo arm, although not without inherent problems, would have aided the unbiased assessments of these more subjective endpoints.

An additional methodological concern was the high dropout rate and disparity in dropout rates between the trial arms. The dropout rate was particularly high early in the trial, and some patients were thought to not fully appreciate the logistic demands of HBO. This was addressed by reinforcing informed consent. Additionally, some trial sites unexpectedly withdrew funding when HBO was reclassified as a clinical trial excess treatment cost. A higher propensity for dropout in the HBO versus the non-HBO arm remained, even after these issues were addressed, reflecting the longer time interval between randomization and treatment for the HBO arm. Despite this, demonstrable comparability between the arms was retained, and a range of sensitivity analyses did not influence the primary analysis.

The HOPON trial confirms the safety of HBO in this patient population. The toxicities related to pressure effects and inspired oxygen percentage were much as expected. Previously, anecdotal concerns over the potential of HBO

Table 3 Visual analogue pain scores at each time point

Assessment	HBO	Non-HBO	Difference (HBO minus standard) in fitted means
Baseline	0.164 (SD = 0.213) Median = 0.063 IQR, 0.011-0.234 N = 67	0.232 (SD = 0.289) Median = 0.074 IQR, 0.02-0.389 N = 69	−0.075 (95% CI, −0.15 to −0.001) *P* = .046
3 months	0.115 (SD = 0.199) Median = 0.02 IQR, 0-0.168 N = 46	0.18 (SD = 0.232) Median = 0.04 IQR, 0.011-0.38 N = 55	−0.057 (95% CI, −0.115 to 0) *P* = .049
6 months	0.116 (SD = 0.206) Median = 0.02 IQR, 0-0.106 N = 51	0.153 (SD = 0.232) Median = 0.03 IQR, 0.011-0.21 N = 54	−0.06 (95% CI, −0.121 to 0) *P* = .049
12 months	0.111 (SD = 0.179) Median = 0.021 IQR, 0-0.168 N = 44	0.252 (SD = 0.299) Median = .101 IQR, 0.011-0.441 N = 48	−0.076 (95% CI, −0.151 to −0.001) *P* = .048

Abbreviations: HBO = hyperbaric oxygen; IQR = interquartile range; SD = standard deviation.

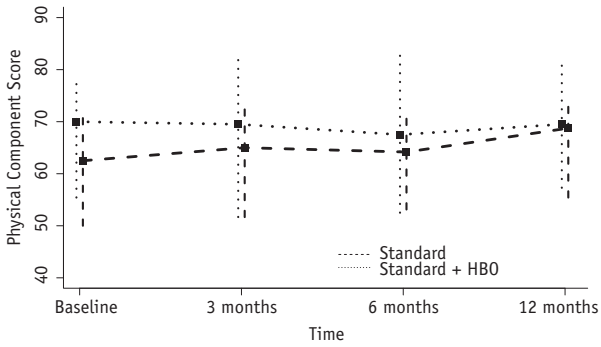

Fig. 3. University of Washington Quality of Life Questionnaire composite physical scores. The physical subscale score is computed as an average of 6 domain scores: chewing, swallowing, speech, taste, saliva, and appearance. A change of 12 units is deemed a large change, and 7.5 units a moderate change. Zero represents the worst possible and 100 the best possible quality of life score.

to reactivate otherwise dormant malignant cells have been raised for patients treated for late radiation effects. In the present trial, subsequent malignancies were notably common, but there were no significant differences in incidence between the HBO and non-HBO trial arms.

Conclusions

In light of the low incidence of ORN in the HOPON trial among patients who were previously considered at high risk, justifying the future use of HBO in the prevention of ORN associated with surgery or dental extraction in the irradiated mandible is difficult. These findings reverse the conclusions of the recently published Cochrane review in this clinical setting. Furthermore, adequately powering any subsequent ORN prevention trial would appear difficult, unless a genuinely high-risk subset of patients could be identified (eg, from biomarkers of susceptibility to severe late radiation effects).[29,30] The significance of temporary improvements in symptoms attributable to the use of HBO remain uncertain, and this would require alternative trial designs to further explore. The financial costs and logistic demands of HBO therapy are very high, and the implications of this trial may include a significant economic saving for health systems where HBO is currently considered a standard of care.

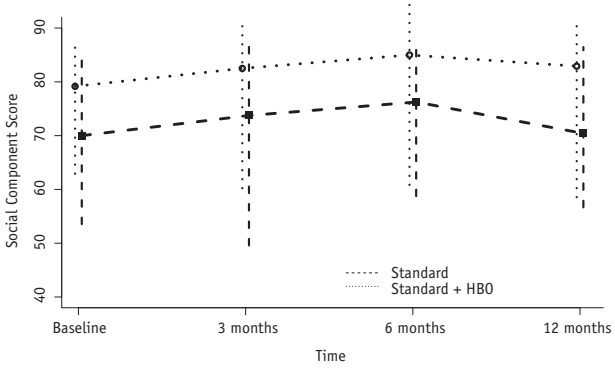

Fig. 4. University of Washington Quality of Life Questionnaire composite social-emotional scores. The social-emotional subscale score is computed as an average of 6 domain scores: anxiety, mood, pain, activity, recreation, and shoulder. A change of 12 units is deemed a large change, and 7.5 units a moderate change. Zero represents the worst possible and 100 the best possible quality of life score.

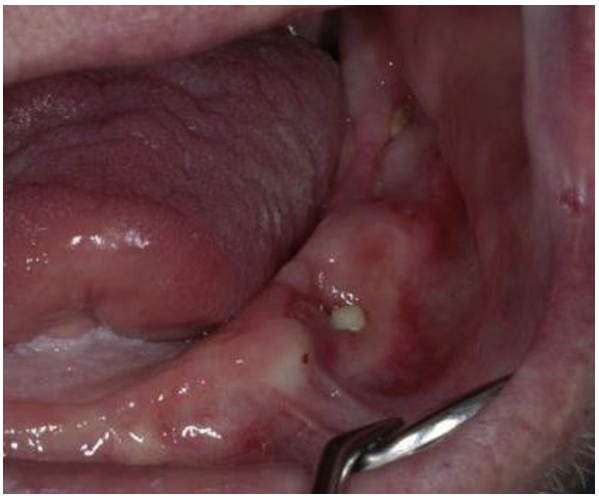

Fig. 5. Clinical photograph of exposed bone. Minor bone spicules with 2 areas of bone <20 mm$^{2(1)}$ in the left posterior mandible 6 months after dental extraction. Minimal bone exposure subject to spontaneous exfoliation and subsequent healing by 12 months.

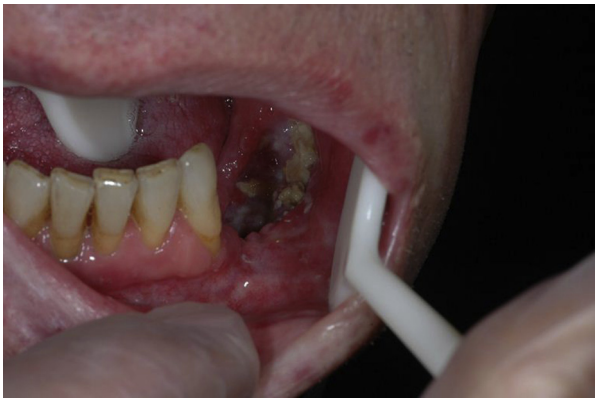

Fig. 6. Clinical photograph of exposed bone. Notani grade 2 osteoradionecrosis in the left posterior mandible 12 months after molar tooth extraction. The area of exposed bone has progressed from Notani grade 1 at 6 months.

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