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Review

Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: treatment

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Abstract

Osteoradionecrosis (ORN) is a serious condition following treatment for head and neck cancer with serious associated morbidity and mortality. While the use of hyperbaric oxygen (HBO) in treating established osteoradionecrosis has been standard practice in many units for years, the evidence base for this remains remarkably weak. The published evidence has been made even more controversial by trial protocols that do not use HBO as it is generally advocated. This review describes the classification, incidence, and treatment of ORN, and explores the available published evidence with particular emphasis on randomised trials of treatment with HBO.

Keywords: Osteoradionecrosis; Hyperbaric oxygen; Randomised controlled trials

Introduction

One of the most feared complications of treatment for head and neck cancer is osteoradionecrosis (ORN) of the jaws. ORN describes the process where irradiated bone undergoes necrosis and becomes exposed through the investing soft tissues. The most important risk factor is surgical trauma, commonly it is dental extractions in an irradiated jaw, but it can also occur spontaneously. It is painful and debilitating, and sometimes requires extensive surgery and even segmental resection. Morbidity and mortality are serious, and treatment outcomes are often unsatisfactory. Hyperbaric oxygen (HBO) was first used in the context of cancer radiotherapy in 1953,[1] but these early reports focused on the re-oxygenation of tumours in an effort to overcome the radioresistance associated with tumour hypoxia. Its use in the management of ORN started in the 1960s, with the earliest published reports by Mainous et al.[2,3] in the early 1970s.

Subsequently, the clinical consensus regarding HBO was largely influenced by Marx et al.[4–6] in the 1980s. Clinical trials have shown objective benefit to late radiation injury such as radiation proctitis,[7] lymphoedema of the arm after axillary radiotherapy for breast cancer,[8] and some cases of ischaemic diabetic ulcers of the lower extremity not treated with radiotherapy.[9] The evidence base for HBO in radiation oncology and late radiation injury is relatively poor, and particularly so in the head and neck, with few randomised trials. We review the current status of HBO in the treatment of ORN with emphasis on evidence from clinical trials.

Definitions, classification, and pathogenesis

The characteristics of ORN are readily recognised, but the exact criteria used to define borderline cases (perhaps to decide on inclusion in clinical trials) are less clear. Diag-

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Table 1
The Notani classification[12] is quickly applicable to all cases of mandibular osteoradionecrosis (ORN) after clinical examination and orthopantogram.

Notani class	Clinical features
I	ORN confined to dentoalveolar bone
II	ORN limited to dentoalveolar bone or mandible above the inferior dental canal, or both
III	ORN involving the mandible below the inferior dental canal, or pathological fracture, or skin fistula

nosis depends on clinical features that include defects in the overlying oral mucosa or skin, and exposed necrotic bone. Associated features[10] of pain, dysaesthesia, malodour, trismus, and a variety of radiographic findings are commonly found in, although not unique to, ORN. Ever mindful of exceptional cases that defy simple rules, a definitive clinical definition of ORN is tentatively suggested as:

"*Exposed and necrotic bone associated with ulcerated or necrotic surrounding soft tissue which persists for greater than three months in an area that had been previously irradiated (not caused by tumour recurrence).*"[11]

Together with the various evolving definitions of ORN, several classifications have been suggested. Some have attempted to derive a classification from Marx's treatment protocol,[4] but this is not universally applicable as it uses the clinical response to HBO and surgical treatments that will not be used in all cases. The classification by Epstein et al.[10] also requires knowledge of the clinical course, distinguishing those actively "progressing" from more chronic "persistent" cases. Instead, we commend a simple, memorable, and immediate classification of mandibular ORN by Notani et al. (Table 1)[12] which does not rely on any knowledge of clinical progress or response to treatment (Figs. 1–4).

The pathogenesis of ORN has not been established with certainty. The theory supporting the role of hypocellularity, hypoxia and hypovascularity support the use of HBO.[6] Alter-

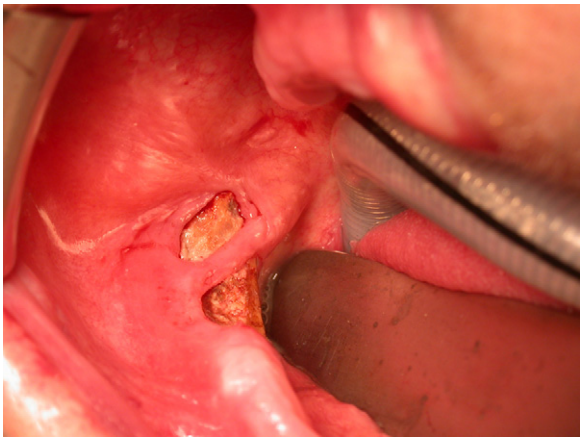

Fig. 1. Notani grade I osteoradionecrosis.

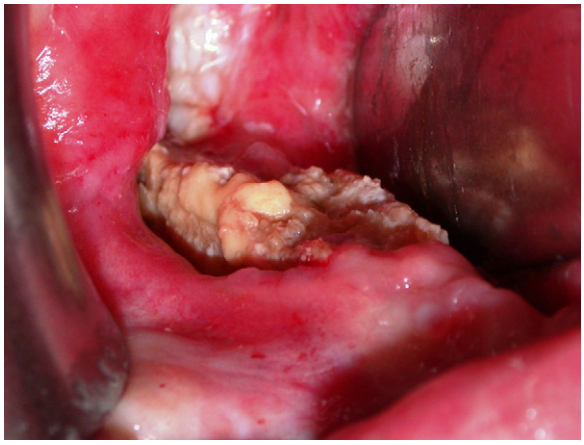

Fig. 2. Notani grade II osteoradionecrosis.

Fig. 3. Notani grade III osteoradionecrosis with soft tissue necrosis, pathological fracture, and orocutaneous fistula.

Fig. 4. Orthopantogram showing Notani grade III osteoradionecrosis with pathological fracture.

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native theories supporting the role of infection or fibrosis have led to other attempts to treat with antibiotics[13] or "antifibrotic" agents.[14] This review will not attempt to add further to a great deal of published speculation about these theories, but aims to evaluate the empirical published clinical evidence and in particular, that of randomised trials.

Evolution of HBO in the treatment of ORN of the mandible

Various treatments have been used in ORN; surgical, conservative, HBO, and others. Reports of good resolution in 15–100% of cases with simple conservative measures such as avoidance of smoking and further trauma, and the use of antibiotics, clarify the necessity for a systematic and measured attitude to aggressive intervention.[2,15–19] An overview of the consensus is that excision of necrotic bone is usually required in more advanced cases. Without doubt the use of composite free flaps has greatly aided reconstruction of the most complex and challenging defects,[20–22] although complication rates for these ambitious operations are higher than for primary reconstruction after tumour ablation. The need for evidence from randomised trials is highlighted by the uncertainty of outcome in untreated and conservatively managed patients. It is also clear that many patients classified as having Notani I ORN after dental extractions could merely have delayed healing of the sockets that would gradually settle over several months. It is crucial to separate these from progressive cases when evaluating published series or clinical trials, and this aspect is frequently overlooked.

Marx's 1983 field-defining report[4] presented the Wilford Hall protocol for HBO in the management of refractory ORN in a retrospective series of 58 cases. Importantly, the cases presented had persistent ORN, and conservative or surgical management, or both, had failed before entering the protocol. As shown in Fig. 5, this protocol is relatively complex and many patients are exposed to 120–150 h of hyperbaric oxygen (some up to 350 h). The paradigm that HBO should only be used in conjunction with surgical removal of necrotic bone is a central feature. The retrospective series describes the resolution of 58 cases of refractory ORN, and the criteria for success are specified as being pain free, having mandibular continuity and function, mucosal healing, and the ability to wear dental prostheses. Later reports by Myers and Marx[23] detail the successful treatment of 268 patients, and others have also found success in this protocol.[24] Subsequently, the logistic and financial limitations of using so many hours of HBO have resulted in many units preferring a simplified protocol of 30 dives before and 10 dives after operation.[25] The use of 30 dives has at least some supporting evidence from human studies,[26] but it is difficult to substantiate claims of one protocol over another because no comparative prospective trials have been done.

In 1999 Marx reported a further 104 patients who required mandibular reconstruction in tissue beds exposed to ≥64 Gy radiotherapy using mesh trays with free bone grafts. The intervention was 20 preoperative and 10 postoperative HBO sessions. Bony continuity was established in 48 of 52 patients for those with HBO compared with 34 of 52 without (RR 1.4; 95% CI: 1.1–1.8; $p = 0.0001$). Few details about any randomisation, or inclusion or exclusion criteria are specified, and the account is only presented within a chapter in a textbook. The largely outdated method of oromandibular reconstruction, and the scant details of the methodology of the trial make the data hard to evaluate. Few centres have succeeded with similar results using such an approach, and now composite free flaps are considered the standard of care.

The optimum therapeutic use of HBO remains poorly understood and this is evident in the lack of standardisation of HBO protocols used by both UK and European chambers.[27,28] The protocols often deviate from the "consensus" Marx protocol of 30 sessions before and 10 sessions after operation at 2.4 atm for 90-min sessions. Most British Hyperbaric Association (BHA) registered chambers only deviate from the Marx protocol in the pressures used, for example a reduction to 2.2 atm, because of anecdotal evidence of fewer complications (transient myopia) at this pressure.[27] The UK chambers not registered with the BHA that are typically used for dubious indications such as the treatment of multiple sclerosis. These use even lower pressures of ≤2 atm, with shorter duration (60 min) and a more variable number of sessions. Fortunately these units only account for 8% of the total number ($n = 273$) of patients treated in the UK by HBO in data recorded over a year. This number is only a subset of the total number of patients with ORN as limited resources severely restrict the availability of such treatment. The opposite trend is found in Europe where 69 chambers reported treating 1304 patients (excluding the UK), and most used higher pressures of 2.5 atm for longer duration/session (more than 90 min), but there were similarities with the number of sessions used.[28]

Randomised controlled trials in HBO to treat osteoradionecrosis of the mandible

To our knowledge the only randomised controlled trial in peer-reviewed publications for the use of HBO in the treatment of ORN in the head and neck region was by Annane et al. in 2004.[29] The trial had many laudable design features: it was a prospective, multi-centre, randomised, double-blind and placebo-controlled study carried out across 12 hospitals with an intended recruitment target of 222. The HBO protocol used 30 dives before and 10 after operation at 2.4 atm for 90 min, and so reflects the contemporary international consensus (if not the Wilford Hall protocol[4]). However, the trial has proved controversial, with several different interpretations of the data possible, and despite serious voiced and published reservations about its design, has eroded enthusiasm for the role of HBO in the treatment of ORN. The principal finding was that HBO did not aid in the management of ORN, indeed an excess of poor outcomes in the HBO

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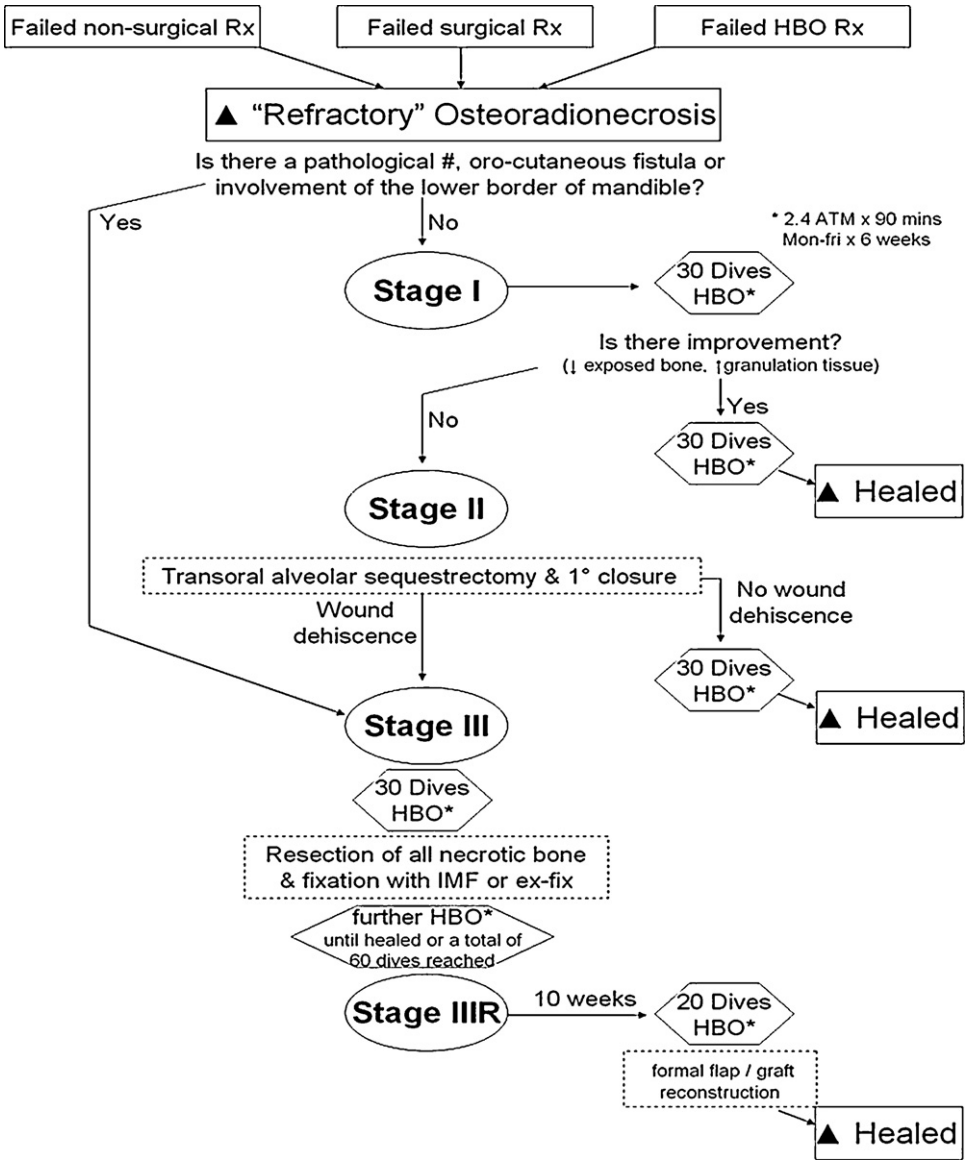

Fig. 5. Wilford Hall hyperbaric oxygen protocol for treatment of osteoradionecrosis.[4]

arm caused premature closure of the trial under early stopping rules. At one year, recovery in the HBO arm was 19%, and 32% in the placebo arm. This finding has now been cited by many health care funding bodies as evidence to withhold reimbursement for its use in the treatment of ORN.

There are three main objections to the trial design. Firstly, the diagnosis, stage, and distribution of patients with ORN entered into the trial have been criticised, and the definition of ORN was imprecise compared with conventional clinical practice. Patients were included in the trial if they had one clinical change and one radiographic change. The clinical changes were pain, dysaesthesia in the distribution of the inferior alveolar nerve, bony exposure, trismus, or fistula. The radiographic changes were increased density, periosteal thickening, diffuse radiolucency, mottled areas of osteoporosis, or sequestration. It can readily be appreciated that many patients who certainly *do not* have ORN would fit within these rather loose criteria. Patients with Notani III ORN[12] (fracture or ORN at the lower border) were excluded from the trial; another factor that limited the usefulness of its findings. Stratification[30] was not used so, of the small number ($n = 68$) actually randomised, a concentration of more severely affected cases could have been assigned to one arm or the other. The importance of this omission is exaggerated by the imprecise inclusion criteria. Interestingly the criteria for the measure of primary outcome were more robust; absence of pain, and exposed bone with stabilisation of radiographic findings. Although this gives confidence as to which patients had "real" ORN at the conclusion of the trial, we do not know who had it at entry. Data in the paper state clearly

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that only 38 of the 68 patients included actually had an area of exposed bone. Can there be confident interpretation of this trial, powered for inclusion of 222 patients, with data based on perhaps 38 "true" cases of ORN?

Secondly, the use of sham HBO has also been controversial. Blinded HBO trials have necessitated the use of a control arm with sham HBO treatments indistinguishable to patients, hyperbaric chamber staff, and head and neck clinicians. The sham HBO in this trial used 9% oxygen and 91% nitrogen so that at 2.4 atm, arterial PaO_2 is similar to breathing 21% oxygen at ambient air pressure. This exposes patients to known risks of decompression dives, and perhaps might be considered unethical in the control group because of the implied issues of safety. Other trials have used 40% oxygen and 60% nitrogen,[31] which expose the patient to higher doses of oxygen, albeit more safely, however providing an alternative lower dose of oxygen treatment and correlation of outcome with oxygen "dose" rather than a true control arm. Also, the provision of sham HBO is at least as costly as conventional treatment which, given finite resources, will reduce the size of the cohort for any trial where resources are limited. The precise details of blinding are not iterated, as often the case in published reports,[32] but it is also debatable whether the HBO chamber staff can ever be effectively blinded. By employing a robust primary endpoint it is probably unnecessary to use sham HBO. Blinded objective assessment of ORN at the conclusion of the trial might be made by post hoc interpretation of clinical photographs and radiographs.

Lastly, and perhaps most importantly, the treatments offered to these patients with diagnosed ORN in the trial did not accord with the established standard of care. In the treatment arm, patients were given HBO treatment twice rather than once daily, which is not supported by previously published protocols. More importantly, the use of HBO alone without operation, does not reflect standard practice. The data seem to show that at least 75% of the treatment group failed to receive the full protocol of 30 sessions. Previous treatment schedules for ORN involve surgical resection of the necrotic bone, and HBO is used as an adjunct[25,33] rather than as the sole or primary treatment. Claims for rejuvenation of dead bone by HBO have generally been avoided, even by advocates of HBO such as Hart and Mainous,[2] and Marx.[4] Annane instead cited the need for definitive surgery *as an outcome criterion*. He defined it as being a failed treatment rather than necessary for all patients.

In summary, this paper provides a fascinating insight into the various hazards that await investigators in the design of clinical trials. It applies non-standard treatment against a non-representative control arm for an ill-defined group of patients who are not typical of the most pressing clinical need. The inclusion criteria are flawed, and one of the primary endpoints is a clinical decision to offer treatment that most specialists view as essential. The value of HBO to patients with ORN has not been proved, and this paper does not offer sufficient quality of evidence in this regard.

HBO in other late radiation effects in the head and neck region

Chondroradionecrosis of the larynx has long been recognised,[34] but is a relatively rare complication of radiotherapy. It has now has assumed greater importance because of renewed enthusiasm for strategies to preserve the larynx with primary concurrent chemoradiotherapy.[35] A common diagnostic dilemma is that residual or recurrent malignant disease may be very hard to distinguish with certainty from chrondroradionecrosis.[36,37] Many retrospective studies suggest that HBO has a beneficial effect,[24,38,39] but they are small and there have been no prospective randomised controlled trials. Osteoradionecrosis of the skull base after treatment for nasopharyngeal or other anatomically related tumours is fortunately very rare.[40–43] The outcome is often fatal, and while surgery and HBO have been suggested, the evidence for benefit is in little more than isolated cases.

The treatment of xerostomia with HBO, and the more generalised effects of HBO on quality of life have been studied in retrospective case series.[44,45] Although it is impossible to discriminate between a true and a placebo effect in these circumstances, modest improvements have been shown in swallowing, taste, and the production of saliva. Clearly these relatively soft endpoints such as patient questionnaires require double-blind, sham-controlled trials to eliminate the placebo effect confidently. Perhaps other more robust endpoints such as volume of saliva measured by Lashley cups, or interincisal opening may be included in future studies.

Alternatives to HBO in the management of late radiation injury

HBO has many disadvantages, not least its expense and the inconvenience of repeated, prolonged treatments. Understandably, alternatives have been sought and medical treatments are clearly more attractive than surgery. The hypothesis by Delanian and Lefaix proposes that ORN may be analogous to the radiation-induced fibroatrophic process seen in soft tissue, which may be partly reversed by combined pentoxifylline-tocopherol treatment.[14] A clinical trial has shown benefit in radiation-induced fibrosis after radiotherapy for breast cancer,[46] but these results have not been reproduced in similar randomised trials from other units,[47] or in other sites in the body.[48] A single uncontrolled and non-randomised case series of patients with mandibular ORN treated with pentoxifylline, tocopherol, and *vitamin E* has been reported by Delanian et al.[49] This series of 18 patients treated from 1995 to 2002 used two different drug protocols within this series, adding clodronate in the latter 8 patients in the series.. While the results show an improvement in the severity of ORN, this small case series remains the only published evidence we know of to date. This interesting report poses a question that needs to be answered within randomised trials.

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Systematic reviews and meta-analyses

Various systematic reviews involving either the management of irradiated head and neck patients or the value of HBO have been completed. The excellent systematic review by Pasquier et al.[50] concluded that the number and proportion of patients in many retrospective series who improved suggests that HBO *could* be effective in the treatment of ORN. A recent Cochrane review[51] concluded that there is some evidence that HBO improves outcome in late radiation tissue injury that affects bone and soft tissues of the head and neck, but emphasised the need for further large randomised trials of "high methodological rigour". The relevant Scottish Intercollegiate Guidelines Network (SIGN) guidelines[52] place research into the role of HBO in irradiated patients among the highest priorities in the head and neck field.

In summary it is difficult to find fault with any of the conclusions of these systematic reviews. Further robust and randomised trials must be supported by researchers in head and neck cancer. It is difficult to recommend the repeated expense of further centrally commissioned meta-analyses when the evidence base is so poor; more benefit would accrue from diverting these resources into prospective trials.

Conflicts of interest

R.J.S. is Chief Investigator of CR-UK HOPON trial and UK Principal Investigator on DAHANCA-21 trial. J.D. has no conflict of interest.

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