

Therapeutic Use of Hyperbaric Oxygen for Irradiated Dental Implant Patients: A Systematic Review

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Abstract: The aim of this systematic review was to investigate the effectiveness of hyperbaric oxygen (HBO) therapy for irradiated patients who require dental implants using data from randomized controlled clinical trials (RCTs). The review was prepared according to Cochrane Collaboration guidelines. The Cochrane Oral Health Group Specialist Register and the Cochrane Controlled Trials Register were searched (Cochrane Library 2002, Issue 2), together with Medline from 1966 or Embase from 1974. Several journals were hand-searched, and fifty-five implant manufacturers were contacted in an attempt to identify ongoing or unpublished studies. The results were that no RCTs comparing HBO with no HBO for implant treatment in irradiated patients were identified. Our principal conclusions are that clinicians ought to be aware and make patients aware of the lack of reliable clinical evidence for or against the clinical effectiveness of HBO therapy in irradiated patients requiring dental implants. There is a need for RCTs to determine the effectiveness of HBO.

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Because healthcare providers, researchers, and policymakers are inundated with unmanageable amounts of information, systematic reviews are designed to provide data for decision-making in a more manageable form.¹ An extensive preclinical animal literature and a multitude of clinical reports about the use of hyperbaric oxygen (HBO) therapy exist, yet there is controversy about its effectiveness for certain conditions. Overzealous claims in the 1960s, later demonstrated to be invalid, that HBO was effective for a multitude of conditions including myocardial infarction and stroke have added to the controversy.² Clinical guidelines have been proposed for HBO use in conjunction with dental implant placement.

Dentures and bridges have traditionally been used to replace teeth to restore mastication, speech,

and appearance. Dental implants offer an alternative for tooth replacement. They are surgically inserted into the mandible or maxilla to support a dental prosthesis and are retained during functional loading because of the intimacy of bone growth onto their surface. This direct anchorage of the implant is referred to as osseointegration.³ Patients who have undergone surgery for orofacial cancer may particularly benefit from implant treatment, as conventional prosthetic treatment may be difficult if the anatomy is less favorable after surgery. However, if the patient also requires radiotherapy, then this implant treatment may be compromised. It has been shown that there is an increased failure of implant treatment with greater loss of implants in irradiated compared to nonirradiated bone, with more losses with longer time intervals between irradiation and implant treatment,

and more losses with greater doses of irradiation.^{4,5} Irradiated tissues lose the capacity for restorative cellular proliferation, leading to decreased vascularity and local hypoxia.⁶

HBO treatment developed from studies carried out by U.S. Navy medicine units investigating the management of decompression sickness and arterial gas embolism. The Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society currently recommend HBO for several uses, including air and gas embolism, carbon monoxide poisoning, clostridial myonecrosis, refractory osteomyelitis, and others (www.uhms.org). The use of HBO for the management of irradiation-damaged tissues was introduced in the 1970s.⁷ HBO was used in oral and maxillofacial surgery for the management of osteoradionecrosis in particular, and an RCT reporting the superiority of HBO over antibiotics strengthened the position of HBO as an important therapy.⁸ This was followed by a proposed protocol using HBO for irradiated patients requiring osseointegrated implants treatment.⁹ HBO therapy consists of exposing the patient to intermittent, short-term, 100 percent oxygen inhalation at a pressure greater than one atmosphere. Typically a patient has approximately twenty treatment sessions, each lasting ninety minutes, prior to implant placement and about ten following placement.

While a protocol has been established, it is not clear whether the clinical evidence supports this HBO therapeutic procedure. The aim of this review was to investigate the effectiveness of HBO therapy for irradiated patients who require dental implants using data from the highest level of evidence: randomized controlled clinical trials (RCTs).

Study Methods

The review was conducted according to the Cochrane Collaboration guidelines and published electronically on the Cochrane Library.¹⁰ The Cochrane Collaboration (www.updatesoftware.com/ccweb/cochrane/cc-broch.htm) is an international network of individuals committed to preparing, maintaining, and disseminating high-quality systematic reviews of RCTs on every sort of healthcare intervention in order to provide the most current and accurate evidence about medical treatments available in the world.¹¹ The Cochrane Collaboration focuses particularly on reviews of RCTs because they are likely to provide more reliable information than other sources of evidence.¹²

The aim of the review was to test the null hypothesis of no difference in success, morbidity, patient satisfaction, and cost-effectiveness between dental implant treatment for irradiated patients with and without HBO. RCTs to be considered for this review were those comparing HBO with no HBO in patients who had undergone radiotherapy and who had missing teeth that required replacement with osseointegrated dental implants.

The following outcome measures were identified to investigate the effectiveness of HBO therapy for irradiated patients who require dental treatment:

- prosthetic failure due to inadequate support because of implant failure;
- implant failure determined by mobility or implant loss;
- changes in marginal bone levels measured on intraoral radiographs;
- adverse effects such as tympanic membrane rupture or pneumothorax;
- mucosal health;
- patient satisfaction; and
- cost-effectiveness.

Development of a comprehensive search strategy was a crucial aspect of undertaking this review to ensure the identification of all randomized controlled trials, in any language, available on Medline since 1966 or Embase since 1974, that described articles comparing HBO with no HBO for patients treated with dental implants. This search strategy used a combination of controlled vocabulary and freetext terms and was revised appropriately for each database. The Cochrane Oral Health Group Specialist Register and the Cochrane Controlled Trials Register (Cochrane Library 2002, Issue 2) were also searched. Indeed, the Cochrane Controlled Trials Register is nowadays likely to be the best single source of published trials for inclusion in systematic reviews.¹³ A comprehensive, unbiased search is one of the key differences between a systematic review and a traditional review.

The following journals were identified as being important to be handsearched for this review: *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *International Journal of Prosthodontics*, *Journal of the American Dental As-*

sociation, *Journal of Biomedical Materials Research*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral Implantology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, and *Journal of Prosthetic Dentistry*. Where these had not already been searched as part of the Cochrane Journal Handsearching Programme, the journals were handsearched by the authors. In addition, in an attempt to identify any unpublished RCTs, fifty-five implant manufactures and three experts in the field of HBO were contacted.

Results

Two of the reviewers independently screened the titles and abstracts of all reports identified from the electronic searches for study design and relevance of the reported intervention. If there was any uncertainty, then the full article was checked.

Following this search of the literature, no RCTs comparing HBO with no HBO for implant treatment in irradiated patients were identified. Letters sent to implant manufacturers and three experts requesting information about studies also failed to identify any relevant RCTs.

Discussion

Irradiation can produce both early and late tissue changes. Early effects include those of salivary glands, skin, and oral mucosa, whereas later effects involve bone changes leading to demineralization, fibrosis, increased susceptibility to infection, and finally, avascular necrosis.⁹ Clinicians are therefore understandably anxious that they do no harm and use the most effective protocol to ensure the highest success when providing implant treatment to aid prosthesis retention to improve the patient's quality of life.

Researchers have recognized the limitations of animal models in providing the best evidence for treatment efficacy. That is because the follow-up periods are very short compared to humans; simulating the radiation fractionating schemes is difficult; and there are different cellular turnover rates.⁹ Of the different designs of clinical studies, the randomized controlled trial is recognized as providing the best evidence for treatment effectiveness.¹⁴ Weaker designs, in general, tend to overestimate treatment effects.¹⁵ Data from trials based on weak designs, such

as uncontrolled case reports, can be misleading and should be given less weight when assessing intervention effectiveness. The level of evidence generated by different study designs¹⁶⁻¹⁹ for evaluating the effectiveness of oral implant therapy can be ranked in the following way:

1. Systematic reviews of original individual patient data
2. Systematic reviews of multiple RCTs
3. RCTs of adequate size
4. Prospective CCTs
5. Retrospective CCTs
6. Noncontrolled clinical trials
7. Case reports
8. Animal studies (indirect evidence)
9. In vitro studies (indirect evidence)

Randomization ensures that all participants have the same chance of being assigned to each of the study groups and, if done properly, reduces the risk of serious imbalance in unknown but important factors that could influence the clinical course of the participants.²⁰ No other study design allows investigators to balance these unknown factors. Nonrandomized controlled clinical trials offer weaker evidence than RCTs because only minimal precautions (stratification and matching) prevent systematic factors influencing the allocation of the subjects in one of the study groups. It was therefore unfortunate that we were unable to identify even a single RCT about dental implant treatment for irradiated patients.

The randomization process can be described as the generation of an unpredictable allocation sequence of the trial participants. To be effective, the randomly generated sequence should be strictly implemented, and maximal attention should be given to avoid any possible source of subversion.²¹ This process is called "allocation concealment" and is designed to prevent foreknowledge of the treatment assignment. The use of a central telephone randomization or sequentially numbered sealed opaque envelopes has been recommended as the minimal measure for allocation concealment.²² There are no barriers to applying this study methodology to the question of HBO effectiveness.

In a review such as this when no RCTs are identified, it is important to recognize that electronic databases are not complete. They do not list all published journals and abstracts, and there is a delay between the publication date and entry of the article on the database. Inadequate labelling of articles has also been identified as a problem.^{23,24} Handsearching of articles, letters, and books is therefore the gold

standard method for identifying all published evidence and, in particular, RCTs. When Cochrane Collaboration staff started handsearching back issues of journals, including non-English language publications, it was found that Medline provided inadequate tagging of RCTs and contained less than half of all published RCTs.²⁵ This information has led to important changes in the National Library of Medicine (NLM), so that trials identified by the Cochrane Collaboration are being retagged and NLM is planning to set up a supplemental database for RCTs not present in Medline.

The ideal RCT should include a strategy for blinding the investigator and patient to control for the effect of the clinician's or patient's expectations. With blinding, group assignments (e.g., intervention/s and control/s) are kept secret from the study participants (single blind) or from both participants and outcome assessors (double blind). Triple blinding requires the statistician to be unaware of participant group assignment. Blinding is used to protect against the possibility that knowledge of assignment may influence the patient response to the treatment, the behavior of the clinician providing the intervention (performance bias), or the outcome assessment (detection bias). However, blinding is not always practical, and it has been argued that it is not possible because of technical difficulties to design a study involving HBO.²⁶ Certainly a patient would be aware of whether they had received treatment in an HBO chamber or not. However, a trial conducted to investigate the benefit of HBO for carbon monoxide poisoning used a true sham control by delivering normobaric oxygen in a hyperbaric chamber²⁷ to avoid this problem. Even without patient blinding, it is possible to arrange for the outcome assessor to be independent and blinded.

Conclusions

Evaluation of the effectiveness of oral health interventions is essential for several reasons, the most important of which is the health benefit and well-being of patients. The question of whether or not HBO is effective for implant success in irradiated patients is important. HBO requires significant patient compliance and involves expensive equipment and cost per patient treatment. Systematic reviews can provide guidance to clinicians and patients about clinical decisions, but the highest quality reviews require assessed RCTs for inclusion. Whilst there are

many scientific articles published about HBO, including a number of narrative review papers, RCTs are lacking.

Clinicians ought to be aware and should make patients aware of the lack of reliable clinical evidence for or against the clinical effectiveness of HBO therapy in irradiated patients requiring dental implants. Not only is there a need for RCTs to determine the effectiveness of HBO, but it is likely that these trials will need to be multicentered as each center may have a limited number of patients. Only with that will clinicians receive the evidence they need to make the best treatment decisions possible.

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