The Role of Hyperbaric Oxygen Therapy on the Management of Mandibular Osteoradionecrosis: A Scoping Review

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Abstract

Osteoradionecrosis is a condition in which the nonvital irradiated bone, fails to heal to over for three to six months, causing the bone to open and disrupt the mucosa or overlying skin without cancer recurrence. Osteoradionecrosis most often occurs at mandibular sites, one of the treatments is hyperbaric oxygen therapy (HBOT) but it's still a contradiction whether HBOT has a good effect or not. This study aims to determine the effectiveness of HBOT in osteoradionecrosis of the mandible.

This scoping review was on studies reporting the use of HBOT in osteoradionecrosis of the mandible. Search for articles refers to Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) through PubMed and Google Scholar that meet the criteria according to the PICO (Population, Intervention, Comparison, Outcome) framework. The filterings were the year published, indexed by Scopus, the title and abstract, and the contents of the entire article.

There were 7 articles related to the administration of HBOT in the treatment of mandibular osteoradionecrosis with the majority as multimodality therapy.

HBOT has a positive role in the healing process of mandibular osteoradionecrosis, especially as a multimodality therapy.

Review (J Int Dent Med Res 2023; 16(4): 1836-1845)

Keywords: Hyperbaric oxygen therapy, mandible osteoradionecrosis, adjunct therapy, multimodality therapy.

Received date: 24 August 2023 **Accept date:** 22 October 2023

Introduction

Head and neck cancer can be cured by either surgery, radiotherapy, chemotherapy, targeted therapy, or a combination.[1] Approximately 75% of head and neck cancer patients require radiotherapy as the main treatment, adjunct to surgery, in combination with chemotherapy, or as palliation.[2] The increase in the incidence of head and neck cancer malignancy relates to the increased use of radiotherapy.[3] Radiotherapy is currently one of the popular treatments for various types of cancer, but radiotherapy can damage normal tissue resulting in short-term and long-term side effects[4] including sialadenitis, mucositis, xerostomia, loss of taste sensation, trismus, tooth hypersensitivity, infection (especially candidiasis), nausea, vomiting, periodontal changes, and skin desquamation.[5–7] Another complication of radiotherapy is an injury to the periosteal blood vessels, decreased osteoblast and osteoclast activity, and increased adipose tissue and fibrotic connective tissue in the bone marrow, resulting in decreased blood vessels and cellularity causing the bone marrow to become hypoxic and bone demineralization that can lead to increased bone fragility and osteoradionecrosis.[7]

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Osteoradionecrosis (ORN) is a non-healing condition in the irradiated area so that the bone becomes necrotic and causes the area to open and disrupt the mucosa or skin that covers it without cancer recurrence.[3,6,8–10]

Clinically, ORN presents as a painful, exposed area of bone with purulent drainage and sometimes progresses to fistula formation (mucosal or skin).[11] ORN occurs when a radiation dose is given >60 Gy. The most common location is the mandible[6], with incidents ranging from 2.6% to 15%. The mandible receives limited blood supply only from the inferior alveolar and facial arteries, which are lesser than the other facial bones.[12] The primary healing process is not different between ORN that occurs in the mandible or maxilla.[13] Marx described the pathophysiology of osteoradionecrosis as an injury to the irradiated area that is difficult to heal. Radiotherapy can damage healthy cells of the vascular endothelium thereby creating conditions of hypoxia, hypocellularity, and hypovascularity making the damaged tissue can no longer repair itself.[14] One treatment that can be done is hyperbaric oxygen therapy (HBOT), but it's still a contradiction whether HBOT has a good effect or not.[15]

There are several staging methods on ORN, with Marx's approach remaining the most extensively used. The approach is based on a sequential treatment strategy in which a patient advances through each level after failing more conservative treatments. Stage I: exposed alveolar bone without pathologic fracture, which responds to hyperbaric oxygen therapy, stage II: disease does not respond to HBOT, and requires sequestrectomy and saucerization, stage III: full thickness bone damage or pathologic fracture, usually requires complete resection and reconstruction with free tissue.[16] Notani classified ORN patients into grades I, II, and III based on the amount of the damage. ORN restricted to the alveolar bone was classified as Grade I. ORN in Grade II was limited to the alveolar bone and/or the jaw above the level of the mandibular alveolar canal. ORN with a cutaneous fistula and/or a pathologic fracture was classified as Grade III.[17,18]

HBOT is the use of 100% oxygen at a pressure greater than normal atmospheric pressure, which is 1 ATA (Absolute Atmosphere), 1 ATA is equal to 760 mmHg.[19–22] HBOT has existed since the 1600s, but for decades, its use was unfounded.[23] HBOT for surgical patients has been known since 1956.[24] HBOT in dentistry is used to help the healing process of mandibular ORN of the mandible, increased intraoral wound healing and symptom improvement.[19,25]

Materials and methods

The first step in conducting a comprehensive systematic review was to define the problem through an organised study. This study was a scoping review using PICO to identify research questions: (1) population: mandibular osteoradionecrosis patients; (2) intervention: administration of HBOT; (3) comparison: none, (4) outcome: HBOT plays a role in the healing process of mandibular osteoradionecrosis.

Inclusion/Exclusion Criteria

The eligibility criteria were determined by inclusion and exclusion criteria. The inclusion criteria in this study were articles discussing the benefits of hyperbaric oxygen therapy, osteoradionecrosis, and osteoradionecrosis of the mandible, published in 2011-2021, written in English and indexed by Scopus. The exclusion criteria were HBOT as a preventive therapy, animal studies, and review articles. Article screening was carried out in four stages, including (1) excluding articles published under 2011; (2) selecting articles indexed by Scopus journals; (3) selecting titles and abstracts that are not relevant; (4) reading the entire contents to see the correlation with the topic. Selected articles were analyzed using thematic methods (identifying, analyzing, and reporting in the form of conclusions).

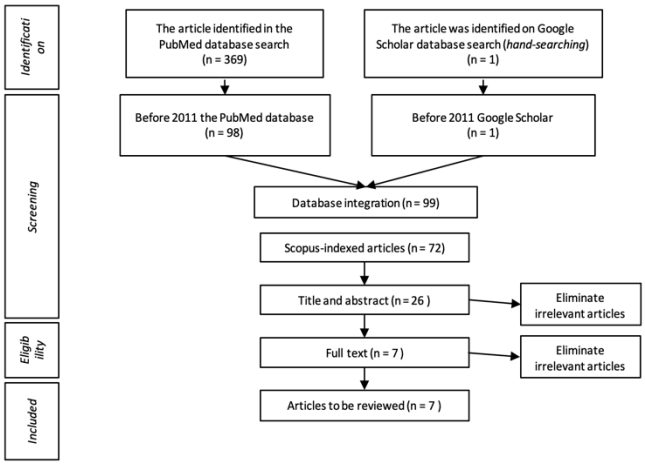

Figure 1. Preferred Reporting Items in Systematic Reviews and MetaAnalyses

(PRISMA) Flowchart

Systematic Literature Search

The data was achieved from the PubMed and Google Scholar search engines indexed by Scopus following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow scheme. The keywords used in the PubMed search engine are "((((hyperbaric oxygen therapy) OR (HOT)) OR (HBOT)) OR (Hyperbaric Oxygen Treatment)) AND ((((((((osteoradionecrosis)) OR (jaw osteoradionecrosis))) OR (osteoradionecrosis of the jaw)) OR (osteoradionecrosis in dentistry)) OR (dental osteoradionecrosis)) OR (Mandibular Osteoradionecrosis)) OR (mandible Osteoradionecrosis))). The search strategy carried out on the Google Scholar search engine used the hand-searching method with the search terms: (1) with all words: osteoradionecrosis, mandible, hyperbaric; (2) with at least one word: adjunctive, efficacy; (3) where the word appears: anywhere in the article; (4) articles dated between 2011 – 2021.

Evaluation of the Included Articles' Quality

The collected articles were subjected to a quality assessment or critical appraisal in order to systematically examine and understand the research's validity, conclusions, and importance. The following criteria were used to assess the research' internal and external validity: descriptive bias, selection bias, measurement bias, analytic bias, and interpretation bias. Three reviewers (not including the authors) independently assessed the quality of all included papers. The National Institutes of Health (NIH) quality assessment criteria were used to determine whether the quality was "good," "fair," or "poor", as shown in Table 1.

Results

From the search results on the PubMed search engine, 369 articles were found and 1 article from the hand-searching on Google Scholar. Initial screening (not been published in the last 10 years and available in full text) resulted in 99 articles. The second screening (indexed in Scopus) obtained 72 articles. The next screening was done by selecting titles and abstracts so that a database of 26 articles was obtained. Articles that were excluded for irrelevant reason, so that the final database was 7 articles.

Gupta et al[25] conducted a study on 33 patients with a history of radiation therapy for head and neck cancer for stage I mandibular ORN based on Marx's classification. HBOT is administered once daily in a multiplace chamber at 2.4 atmospheres absolute pressure (ATA) for 90 minutes, 6 days a week for up to 30 consecutive sessions along with wound care and supportive care. The study showed that 16 patients (48%) had complete wound healing, 6 patients (18%) showed significant improvement, 8 patients (24%) had slight improvement, and 3 patients (9%) had no change. The HBOT resulted in a significant reduction in pain (70%), improvement in eating ability, reduced oral dryness, improved speaking and improved speech and jaw opening. Changes in overall well-being as 'good' recovery was observed in 33% (n = 11), 'moderate' recovery in 52% and 'poor' recovery in 15% (n = 5) cases. The poor recovery may be due to 3 patients only performing HBOT without continuing surgical treatment, one patient receiving irregular HBOT sessions, and one patient having tumour recurrence.

Author(s) (Year)	Study Design	Title	Sample	Method		Result	Biased Examination
				HBOT Treatment	Other Treatment		
Gupta et al.[25] (2013)	Retrospective Study	A Retrospective Study of Outcomes in Subjects of Head and Neck Cancer Treated with Hyperbaric Oxygen Therapy for Radiation-Induced Osteoradionecrosis of Mandible at a Tertiary Care Centre: An Indian Experience	n = 33 mandibular ORN patients (Marx stage 1)	100% O_2 2.4 ATA, 90 mins, 30 sessions, six days every week	Conservative care, wound care, and supportive care.	a) Intraoral wound healing. - Complete = 48% - Significant = 18% - Slight = 24% - No change = 9% b) Improvement of symptoms - Pain reduction = 70% - Eating ability = 52% - Dryness = 71% - Speaking = 41% - Jaw opening = 62% c) Overall Welfare Change - Good = 33% - Enough = 52% - Bad = 15%	Good

Jenwitheesuk et al.[6] (2018)	Retrospective Study	Efficacy of Adjunctive Hyperbaric Oxygen Therapy in Osteoradionecrosis	n = 84 mandibular ORN patients (all stages)	100% O_2 2.4 ATA Duration = 90 mins Total sessions = 30 (20 before and 10 after the action)	Tooth extraction for stage 1 and 2 mandibular ORN and bone debridement for stage 3	HBOT plays a significant role in stage 1 and 2 mandibular ORN. Stage 3 mandibular ORN has a negative correlation with the amount of HBOT administration.	Good
Jenwitheesuk et al.[26] (2021)	Case-control study	Is Adjunctive Hyperbaric Oxygen Treatment Alone or with Surgery the Proper Management for Active and Persistent Osteoradionecrosis ?	n = 61 Active, persistent, or stage III Marx. mandibular ORN	O_2 level = 100% O_2 Pressure = 2.4 ATA Duration = 90 mins Total sessions = 40 (30 before and ten after surgery)	Antibiotics and sequestrectomy, bone resection and reconstruction, reconstruction of fascia, or muscle flaps, fistulectomy.	30 patients recovered 31 patients did not recover during the study period with nine delayed operations	Good
Dieleman et al.[10] (2016)	Retrospective Study	The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible	n = 27 (all stadiums Notani et.al)	O_2 level = 100% O_2 Pressure = 2.4 ATA Duration = 90 mins Total sessions = 40 (30 sessions before and ten after surgery)	HBOT followed by surgical debridement and antibiotics before surgery	Recovered after HBOT only = 3 cases HBOT and surgery = 15 cases Requires next operation = 12 cases The patient has stable disease = 1 case With final result = 11 stage 1 = all healed 8 stage 2 = all healed	Good
D'Souza et al.[17] (2014)	A Retrospective chart	Changing trends and the role of medical management of the mandible: experience from a regional head and neck unit	n = 71 All Notani stadiums HBOT Stage I = 9 Stage II= 8 Stage III= 11	N/A	Flap free reconstruction	HBOT only Stage I = 5 cured, three stable, 1 ORN Stage II = 5 cured, 3 ORN Stage III = 2 cured, six stable, 3 ORN Partially with free flap reconstruction Stage I = 1 out of 1 cured Stage II = 5 out of 6 cured, 1 ORN Stage III = 2 out of 8 cured, six stable	Good
Skeik et al.[27] (2014)	A retrospective review	Hyperbaric Oxygen Treatment Outcome for Different Indications from a Single Center	Mandibular ORN n = 23	O_2 level = 100% O_2 Total sessions = median 30 (24-40 sessions) over 39-64 days	N/A	The condition of mandibular ORN had the highest success rate of 95.7%, and only 1 out of 23 patients failed to respond to HBOT administration.	Good
Hampson et al.[28] (2011)	Prospective Assessment	Prospective Assessment of Outcomes in 411 Patients Treated With Hyperbaric Oxygen for Chronic Radiation Tissue Injury	Chronic radiation tissue injury n = 411	100% O_2 , 2.36 ATA, 90 mins Total sessions = 30 – 60 treatments maximum	N/A	Positive results in 94% of mandibular ORN patients with 73% cured, and 21% significantly improved	Good

Table 1. Research Data Related To Hyperbaric Oxygen Therapy And Mandibular Osteoradionecrosis.

Jenwitheesuk et al[6] conducted a study of 84 patients with mandibular ORN comprised of stage I (n = 53), stage II (n = 7), and stage III (n = 24). The surgical procedure for patients with stage I and II mandibular ORN was tooth extraction, while stage III was bone debridement. All of the patients got 2.4 ATA-90 minutes HBOT in the monoplace chamber as additional prophylactic therapy every day for 20 sessions before undergoing surgery and 10 sessions after the surgical procedure. HBOT had a significant role in improving wound healing in patients with stage I and II mandibular ORN. Stage III mandibular ORN showed a negative correlation with the number of HBOT sessions (p = 0.001, incidence ratio = 0.85). Stage II mandibular ORN required more sessions of HBOT, whereas stage III required fewer sessions because had been initiated with the debridement.

Jenwitheesuk et al[26] conducted a retrospective case-control study for patients diagnosed with stage III mandibular ORN. The three main treatments are specific surgical treatment, HBOT, and antibiotics. The surgical included sequestrectomy, bone resection and reconstruction, reconstruction of fascia or muscle flaps, and fistulectomy. The patients were administered HBOT according to Marx's protocol (HBOT daily at 2.4 ATA for 90 minutes in a monoplace chamber for 30 days before surgery

and 10 after surgery). Of the 61 stage 3 ORN patients, 30 recovered and 31 did not recover. Nine patients from the group who did not recover decided not to have surgery and believed that HBOT alone could solve the problem. Jenwitheesuk et al[26] concluded that HBOT alone was not sufficient for healing. HBOT only improved in terms of reducing pain, swelling, wound repair, and wound size but did not completely cure mandibular ORN.

Dieleman et al[10] conducted a study to evaluate the efficacy of HBOT and surgery in the treatment of mandibular ORN. Twenty-seven ORN patients who had a history of primary oral or tongue base cancer were treated with a radiation dose of 50 Gy. HBOT was administered in 30 preoperative and another 10 sessions of HBOT were administered if the HBOT alone the lesion did not heal. Eleven of the 27 cases of mandibular ORN were Notani stage I, 8 were stage II, and 8 were stage III. An important finding of this study was that HBOT appeared to be useful for stage I and II mandibular ORN, but maybe less useful for stage III. Stage III mandibular ORN were successfully treated by extensive surgery. Based on the results of this study, HBOT can be recommended for stage I and II mandibular ORN and certain cases of stage III.

D'Souza et al[17] conducted a retrospective review study on 71 patients with mandibular ORN at all stages according to Notani et al.[18] The study was conducted by comparing the initial conservative treatment consisting of debridement and HBOT with medicament management. It was concluded that HBOT gave positive results in stages I and II either as a single therapy or a combination with free flap reconstruction. Only one patient in stage II had a recurrence. However, in stage III, HBOT healed only four patients.

Skeik et al[27] conducted a retrospective review of mandibular ORN patients receiving HBOT. Mandibular osteoradionecrosis had a success rate of 95,7% and only 1 out of a total of 23 patients failed to respond to HBOT administration. This study also presents a systematic review of 14 published studies that found that 84% of 371 patients with mandibular ORN showed improvement after HBOT.

Hampson et al[28] performed a prospective assessment in 411 patients treated with HBOT for chronic radiation tissue injury. HBOT is administered at 2 - 2.36 ATA for 90 minutes. Patients received 20 preoperative care and 10 postoperative care. Outcomes of treatment were classified into: 1) cured (90-100% improved); 2) significantly improved (50-89% experienced improvement); 3) improved (0-49% experienced improvement); 4) no change (0% improvement); and 5) worse. This study showed that 59% of patients recovered, 28% of patients were significantly improved, 7% of patients were improved, and 6% of patients were not repaired. No patients got worsened during therapy.

Discussion

Radiotherapy is one of the treatment modalities for head and neck cancer that uses high doses of radiation to target cancer cells and shrink tumours, but it may also damage normal cells surrounding the irradiated cancer cells[29], but it may also damage normal cells surrounding the irradiated cancer cells.[30] Radiotherapy causes the fibroblastic activity to be activated and dysregulated, resulting in tissue atrophy.[31] Radiotherapy can potentially damage endothelial cells directly or indirectly by affecting the formation of reactive oxygen species (ROS).[32] Endothelial cells that have been injured create chemostatic cytokines, which cause an initial inflammatory response and the generation of ROS.[31] Endothelial cell destruction combined with vascular thrombosis can result in endarteritis, blood circulation disruption, constriction of the arterial lumen, a decrease in oxygen and nutrients, and hypoperfused, hypoxic, hypovascular, and hypocellular tissues. This is the primary mechanism for persistent tissue damage.[28] Microvascular necrosis, local ischemia, and tissue loss can all be caused by radiotherapy.[2]

ROS-mediated cytokines including tumour necrosis factor (TNF-a), platelet-derived growth factor (PDGF), fibroblast growth factor-B, interleukins 1, 4, and 6, transforming growth factor B1 (TGF-1) and connective tissue growth factor triggers irregular fibroblasts and maintain a myofibroblast phenotype[2,15] characterized by very high rates of proliferation, secretion of abnormal products from the extracellular matrix, and decreased ability to degrade it.[31] The imbalance between synthesis and degradation in irradiated tissue is most pronounced in bone.[15] The failure of osteoblasts to repopulate and overproliferate myofibroblasts following

irradiation can diminish bone matrix and cause it to be replaced by fibrous tissue.[2,15] ORN microradiography analysis reveals four possible mechanisms of bone destruction: progressive osteoclast resorption mediated by macrophages without osteogenesis; periosteocytic lysis, a pathognomonic feature of osteoradionecrosis; extensive demineralisation caused by external stimuli such as saliva and bacterial products; and accelerated bone ageing.[31] Even decades after radiotherapy, myofibroblasts suffer apoptosis. ORN is caused by fragile cellular tissue with aberrant myofibroblasts.[33] Mandibular ORN occurs following radiotherapy for head and neck cancer, which is frequently performed in the mandibular area.[34]

The Marx classification of mandibular ORN is divided into three stages based on therapy response, such as HBOT. Stage I includes exposed alveolar bone with no pathological fractures that respond to HBOT; stage II does not respond to HBOT and necessitates sequestrectomy and cauterisation; and stage III consists of full-thickness bone damage or pathologic fractures that necessitate complete resection and reconstruction with free tissue.[35] Notani classified mandibular ORN into three stages: stage I (alveolar bone primarily), stage II (alveolar bone and/or mandible above the inferior alveolar canal), and stage III (mandible below the inferior alveolar canal, skin fistula, and/or pathological fracture).[18,36]

ORN-related risk factors, which include the primary site of cancer (more commonly the posterior mandible due to its dense bony nature), the proximity of the tumour to the bone, how far the mandible is included in the primary radiation field, poor oral hygiene including odontogenic and periodontal disease, state of dentition, radiation dose above 60 Gy, nutritional status, concomitant chemo-radiation, chronic trauma from poorly-tailored prostheses, and acute trauma following jaw surgery.[16]

Some hypotheses contend that ORN is a complicated metabolic and tissue homeostatic insufficiency caused by radiation-induced cellular destruction rather than an underlying infection of the irradiated bone. Meyer suggested a radiation, trauma, and infection hypothesis and reported that oral microbial flora penetrates the underlying irradiated bone following injury.[37] Endothelium, bone, and periosteum have all been demonstrated to become hypoxic, hypocellular, and hypovascular as a consequence of ORN.[38] The typical sequence of radiation, trauma, and infection, according to this idea, can be replaced by a series of metabolic and cellular alterations in which cellular death and collagen lysis outweigh synthesis and cellular multiplication, leading to chronic non-healing wounds.[39]

An intriguing concept known as the "fibro-atrophic theory" has recently emerged, and it argues that in response to radiation exposure, fibroblast populations not only suffer total cellular destruction but also show a diminished ability to synthesise and secrete collagen into the surrounding tissue. This approach relies on the idea that osteoclasts are damaged by radiation before vascular changes develop.[37,40] As a result, the stimulation and deregulation of fibroblastic activity, which leads to atrophic tissue inside a previously irradiated area, is the fundamental event in the course of ORN.[37] The prefibrotic phase, constitutive organised phase, and late fibroatrophic phase are the histopathologic phases of ORN development. Changes in endothelial cells are predominant in the initial prefibrotic phase, along with the acute inflammatory response; in the constitutive organised phase, abnormal fibroblastic activity predominates, and the extracellular matrix is disorganised; and in the late fibroatrophic phase, tissue remodelling occurs, along with the formation of fragile healed tissues, which carry a serious inherent risk of late reactivated inflammation in the event of local injury.[16,40]

Endothelial cells get damaged after radiotherapy due to both direct radiation damage and indirect damage caused by radiation-generated reactive oxygen species or free radicals. Injured endothelium cells produce chemotactic cytokines, which initiate an initial inflammatory response and cause polymorphs and other phagocytes to release reactive oxygen species. Endothelial cell degeneration, along with vascular thrombosis, results in microvessel necrosis, local ischemia, and tissue loss. When the natural endothelial cell barrier fails, different cytokines are released, causing fibroblasts to transform into myofibroblasts.[16]

ORN treatment can be challenging and not always successful due to a lack of appropriate, effective methods corresponding to the varied lesions of the oral cavity and jaw, as well as various risk factors. ORN of the jaw is usually treated conservatively or surgically.

During infectious periods, conservative treatments include periodic saline irrigation and antibiotic medicines. Hyperbaric oxygen therapy (HBOT) is another conservative technique. These options for therapy are determined based on the stages of ORN, with a focus on the effective treatment of early and advanced ORN. Stage I ORN is treated conservatively with therapy such as local wound care, HBOT, and antibacterial medicines. Stage III ORN is surgically treated with broad excision and immediate microvascular reconstruction. It is difficult to offer a definitive treatment procedure for stage II, moderate stage ORN.[16,30,41,42]

Antibiotics should always be started following bacterial identification and sensitivity testing, and surgical delays should be avoided. Until bacterial identification is available, penicillin plus metronidazole or clindamycin is usually used. Previous clinical studies have demonstrated that the polymicrobial character of ORN results in a microflora range that is highly sensitive to the therapy regimens often used to treat odontogenic infections. Wound debridement, which involves the removal of infected and devitalized teeth and associated soft tissues, sequestrectomy, which involves the removal of devitalized bony fragments or an involucrum of the jaw, decortication, which involves the removal of lateral and inferior cortical plates of bone to gain access to the infected medullar cavity, and resection with health bony margins with immediate or delayed reconstruction.[16,41]

HBOT is widely believed to improve surgical outcomes by stimulating angiogenesis in irradiated tissues. HBOT not only improves the oxygen supply in hypoxic tissue, causing fibroblastic proliferation and capillary development, but it also improves tissue vascularity, viability, and regenerative capacity. HBOT generates these outcomes most likely by an intricate number of alterations in impacted tissues. The osmotic physiological effect of oxygen presumably reduces tissue swelling, and the steep oxygen gradient generated across an irradiated tissue edge promotes the formation of new blood vessels. Furthermore, increasing oxygen levels promotes white blood cell and fibroblast function, which aids in wound healing.[16]

Administration of 100% oxygen at a pressure of 2.4 atmospheres increases the oxygen pressure in the blood up to 17 times.[43] Dalton and Henry's theory shows how the physiological effects of HBOT alter the oxygen concentration in plasma and help hemoglobin reach its full oxygen-carrying capacity.[44] Henry stated that the amount of oxygen that can be dissolved in the plasma is proportional to the partial pressure of oxygen (PO2).[45] The oxygen-carrying capacity of blood depends on the oxygen bound to hemoglobin and the dissolved oxygen in the plasma, one gram of hemoglobin can bind 1.39 mL of oxygen. The amount of oxygen that can be dissolved in the plasma is proportional to the partial pressure of oxygen (PO2). HBOT dramatically increases the partial pressure of oxygen resulting in the increased dissolved oxygen component in the blood. The dissolved oxygen fraction under hyperbaric conditions may be as 20 times higher than in normal conditions.[44] During HBOT, oxygen pressure in arterial blood can increase up to 2000mmHg (~266.6 kPa)[46] causing increased blood and tissue oxygen levels, infection control, stimulation of angiogenesis, increased collagen deposition, and reduced edema and inflammation.[46,47]

HBOT increases oxygen supply and stimulates neovascularization[25] but has a side effect of the increase of reactive species production which can be positive or negative effects depending on intracellular concentration and localization.[48] HBOT stimulates fibroblast proliferation, and stem cell activation[8,43], restores impaired leukocyte function. The production of ROS, reactive nitrogen species (RNS), and nitric oxide (NO) plays a role in VEGF synthesis[48] so theoretically it contributes to promoting wound healing as well as bone remodelling.[49] HBOT is rarely used as the sole treatment modality but is more commonly used as a surgical adjunct.[50]

Based on the present review, two studies were conducted in uncategorized ORN. The study by Skeik showed that HBOT as adjunctive therapy gave excellent results to 95.7% of mandibular ORN patients.[27] Meanwhile, the study of Hampson et al reported positive results in 94% of mandibular ORN patients.[28]

Five articles classifying mandibular ORN into 3 stages, gave positive results in each stage after administration of HBOT. Stage I gave the best results (Gupta et al[25], Jenwitheesuk et al[6], Dieleman et al[10] and D'Souza et al[17]) to the administration of HBOT, especially as stage I was the multimodality therapy. HBOT is not effective as a single therapy in stage II but it

gives good results when followed by minimal surgical treatment. Dieleman et al[10] showed that stage II only experienced an improvement in symptoms when HBOT was administered with antibiotics and surgical debridement. Jenwitheesuk et al[6] used HBOT as additional prophylaxis before and after tooth extraction. D'Souza et al[17] recommended the addition of free flap reconstruction to HBOT. The lesions in stage II began to be more severe and there was the development of a sequestrum, so other treatments such as conservative and minimal surgery were needed. HBOT alone is not recommended at stage III but requires other treatments, especially extensive surgery. It is following the study of Jenwitheesuk et al[26] which stated HBOT improved only in terms of decreasing pain, swelling, repair of lesions, and size of the lesion. Mandibular ORN was not completely healed and recommended other treatment modalities including antibiotics and extensive surgical treatment such as sequestrectomy, bone resection and reconstruction, fascia or muscle flap reconstruction, and fistulectomy. Dieleman et al and D'Souza et al showed that stage III did not respond to HBOT alone. The optimal results will be achieved when HBOT is combined with extensive therapy, because this stage has a very severe and complex level of damage with the presence of an overall loss of mandibular bone density, fistula or may be followed by pathological fracture. HBOT only acts as an additional therapy that promotes and helps the healing process after surgery.

According to Marx, mandibular ORN is a complex tissue metabolic deficiency caused by radiation-induced cellular injury with the formation of hypoxic, hypocellular, hypovascular tissue, and persistent hypoxia-driven tissue damage that can lead to chronic irreversible injury. Hypoxia can be defined as tissue that fails to receive adequate amounts of oxygen. The term hypoxia quantitatively relates to organs, tissues, and even cell types. The state of hypoxia indicates an oxygen imbalance so that basic functions are disrupted. The tissue damage in mandibular ORN is driven by hypoxia.

HBOT alone usually can not heal the ORN because HBOT can only be compromised by living tissue. So necrotic bone or damaged soft tissue must still be removed with conservative therapy (irrigation, antibiotics, and local debridement). Therefore, HBOT is an adjunct therapy and not a “stand-alone” therapy.[36,45] The administration of HBOT alone does not eliminate the need to complete the healing process with conservative therapy (irrigation, antibiotics, and local debridement) or surgery. Local or surgical debridement is used to clean or remove necrotic bone, as all necrotic bone needs to be removed. This is consistent with research data suggesting HBOT plays an optimal role when given as a multimodality therapy.

The limitation of this study is that the majority of articles are retrospective studies of mandibular osteoradionecrosis with HBOT. The existence of these limitations can be used as an opportunity for further experimental research that can clinically prove the role of HBOT in the healing process of mandibular osteoradionecrosis.

Conclusions

Beyond the limitation of this present review, it can be concluded that HBOT has a positive role in the healing process of mandibular ORN, especially as a multimodality treatment. HBOT plays a positive role in each stage of mandibular ORN. HBOT gives the best result in stage I ORN. HBOT combined with minimal surgery gives good results in stage II mandibular ORN. Extensive surgery is needed when HBOT is administered in stage III ORN to assist in repair, control symptoms, and promote the healing process.

Acknowledgements

The authors would like to express our special thanks of gratitude to the former Head of Indonesian Naval Dental Institute R.E. Martadinata, First Admiral Dr. Ganesha Wandawa, DDS, Periodontist and recent Head of Indonesian Naval Dental Institute R.E. Martadinata, First Admiral Agus Gamal Putra, DDS, Periodontist for the facilities and supports in executing the present study.

Declaration of Interest

The authors report no conflict of interest.

References

1. So WKW, Chan RJ, Chan DNS, et al. Quality-of-life among head and neck cancer survivors at one year after treatment - A systematic review. *Eur J Cancer*. 2012;48(15):2391-2408. doi:10.1016/j.ejca.2012.04.005
2. Spijkervet FKL, Brennan MT, Peterson DE, Witjes MJH, Vissink A. Research Frontiers in Oral Toxicities of Cancer Therapies: Osteoradionecrosis of the Jaws. *J Natl Cancer Inst - Monogr*. 2019;2019(53):86-94. doi:10.1093/jncimonographs/lgz006
3. Shaw RJ, Butterworth CJ, Silcocks P, et al. 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. *Int J Radiat Oncol Biol Phys*. 2019;104(3):530-539. doi:10.1016/j.ijrobp.2019.02.044
4. Wei J, Wang B, Wang H, et al. Radiation-Induced Normal Tissue Damage: Oxidative Stress and Epigenetic Mechanisms. *Oxid Med Cell Longev*. 2019;2019. doi:10.1155/2019/3010342
5. Agarwal P, Upadhyay R, Agarwal A. Radiotherapy complications and their possible management in the head and neck region. *Indian J Dent Res*. 2012;23(6):843. doi:10.4103/0970-9290.111293
6. Jenwitheesuk K, Mahakkanukrauh A, Punjaruk W, et al. Efficacy of Adjunctive Hyperbaric Oxygen Therapy in Osteoradionecrosis. *Biores Open Access*. 2018;7(1):145-149. doi:10.1089/biores.2018.0019
7. Ahadian H, Yassaei S, Bouzarjomehri F, Targhi MG, Kheirollahi K. Oral complications of the oromaxillofacial area radiotherapy. *Asian Pacific J Cancer Prev*. 2017;18(3):721-725. doi:10.22034/APJCP.2017.18.3.721
8. Raggio BS, Winters R. Modern management of osteoradionecrosis. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26(4):254-259. doi:10.1097/MOO.0000000000000459
9. Sultan A, Hanna GJ, Margalit DN, et al. The Use of Hyperbaric Oxygen for the Prevention and Management of Osteoradionecrosis of the Jaw: A Dana-Farber/Brigham and Women's Cancer Center Multidisciplinary Guideline. *Oncologist*. 2017;22(11):1413-1413. doi:10.1634/theoncologist.2016-0298erratum
10. Dieleman FJ, Phan TTT, van den Hoogen FJA, Kaanders JHAM, Merkx MAW. The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible. *Int J Oral Maxillofac Surg*. 2017;46(4):428-433. doi:10.1016/j.ijom.2016.12.004
11. Strojan P, Hutcheson KA, Eisbruch A, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. *Cancer Treat Rev*. 2017;59:79-92. doi:10.1016/j.ctrv.2017.07.003
12. O'Dell K, Sinha U. Osteoradionecrosis. *Oral Maxillofac Surg Clin North Am*. 2011;23(3):455-464. doi:10.1016/j.coms.2011.04.011
13. Dai T, Tian Z, Wang Z, Qiu W, Zhang Z, He Y. Surgical management of osteoradionecrosis of the jaws. *J Craniofac Surg*. 2015;26(2):e175-e179. doi:10.1097/SCS.0000000000001445
14. Leonetti JP, Weishaar JR, Gannon D, Harmon GA, Block A, Anderson DE. Osteoradionecrosis of the skull base. *J Neurooncol*. 2020;150(3):477-482. doi:10.1007/s11060-020-03462-3
15. Dhanda J, Pasquier D, Newman L, Shaw R. Current Concepts in Osteoradionecrosis after Head and Neck Radiotherapy. *Clin Oncol*. 2016;28(7):459-466. doi:10.1016/j.clon.2016.03.002
16. Fan H, Kim SM, Cho YJ, Eo MY, Lee SK, Woo KM. New approach for the treatment of osteoradionecrosis with pentoxifylline and tocopherol. *Biomater Res*. 2014;18(1). doi:10.1186/2055-7124-18-13
17. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: Experience from a regional head and neck unit. *Br J Oral Maxillofac Surg*. 2014;52(4):356-362. doi:10.1016/j.bjoms.2014.01.003
18. Notani K ichi, Yamazaki Y, Kitada H, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck*. 2003;25(3):181-186. doi:10.1002/hed.10171
19. Wandawa G, Mustaqimah DN, Sidik S, Saraswati H, Putri FA, Auerkari EI. Efficacy of hyperbaric oxygen therapy as an adjunctive therapy of chronic periodontitis. *J Int Dent Med Res*. 2017;10(1):72-76.
20. Brahmanta A, Prameswari N. VEGF regulates osteoblast differentiation in tension and pressure regions orthodontic tooth movement administered with hyperbaric oxygen therapy. *J Int Dent Med Res*. 2019;12(4):1382-1388.
21. Irmaleny, Sitam S, Pribadi S, Dewi PY. The Role of HBOT on Pulp Capping Treatment in Enhancing TGF-β Levels: Scoping Review. *J Int Dent Med Res*. 2022;15(3):1352-1358.
22. Ashrin MN, Sari RP, Andriani D. Hyperbaric Oxygen Therapy Reduces Inflammation in Nickel Hypersensitivity. *J Int Dent Med Res*. 2022;15(2):587-593.
23. Lam G, Fontaine R, Ross FL, Chiu ES. Hyperbaric oxygen therapy: Exploring the clinical evidence. *Adv Ski Wound Care*. 2017;30(4):181-190. doi:10.1097/01.ASW.0000513089.75457.22
24. Dauwe PB, Pulikkottil BJ, Lavery L, Stuzin JM, Rohrich RJ. Does hyperbaric oxygen therapy work in facilitating acute wound healing: A systematic review. *Plast Reconstr Surg*. 2014;133(2):208-215. doi:10.1097/01.prs.0000436849.79161.a4
25. Gupta P, Sahni T, Jadhav GK, Manocha S, Aggarwal S, Verma S. A Retrospective Study of Outcomes in Subjects of Head and Neck Cancer Treated with Hyperbaric Oxygen Therapy for Radiation Induced Osteoradionecrosis of Mandible at a Tertiary Care Centre: An Indian Experience. *Indian J Otolaryngol Head Neck Surg*. 2013;65(SUPPL 1):140-143. doi:10.1007/s12070-013-0640-z
26. Jenwitheesuk K, Mahakkanukrauh A, Punjaruk W, et al. Is adjunctive hyperbaric oxygen treatment alone or with surgery the proper management for active and persistent osteoradionecrosis? *Adv Ski Wound Care*. 2021;34(2):1-4. doi:10.1097/01.ASW.0000725164.18431.a7
27. Skeik N, Porten BR, Isaacson E, et al. Hyperbaric oxygen treatment outcome for different indications from a single center. *Ann Vasc Surg*. 2015;29(2):206-214. doi:10.1016/j.avsg.2014.07.034
28. Hampson NB, Holm JR, Wreford-Brown CE, Feldmeier J. Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury. *Cancer*. 2012;118(15):3860-3868. doi:10.1002/cncr.26637
29. Dumoulin S, van Maanen A, Magremanne M. Dental prevention of maxillo-mandibular osteoradionecrosis: A ten-year retrospective study. *J Stomatol Oral Maxillofac Surg*. 2021;122(2):127-134. doi:10.1016/j.jormas.2020.05.022
30. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: A systematic review. *Int J Oral Maxillofac Surg*. 2011;40(3):229-243. doi:10.1016/j.ijom.2010.10.005
31. Darshan K, Vasudeva CI, Poonja P. Osteoradionecrosis: A Review. *ARC J Dent Sci*. 2019;4(2):14-17. doi:10.20431/2456-0030.0402004
32. Ceponis P, Keilman C, Guerry C, Freiberger JJ. Hyperbaric oxygen therapy and osteonecrosis. *Oral Dis*. 2017;23(2):141-151. doi:10.1111/odi.12489
33. Gevorgyan A, Wong K, Poon I, Blanas N, Enepekides DJ, Higgins KM. Osteoradionecrosis of the mandible: A case series at a single institution. *J Otolaryngol - Head Neck Surg*. 2013;42(SEP):1-7. doi:10.1186/1916-0216-42-46
34. Opasanon S, Pongsapich W, Taweepraditpol S, Suktitipat B, Chuangsuwanich A. Clinical effectiveness of hyperbaric oxygen therapy in complex wounds. *J Am Coll Clin Wound Spec*. 2014;6(1-2):9-13. doi:10.1016/j.jccw.2015.03.003
35. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *Int Dent J*. 2018;68(1):22-30. doi:10.1111/idj.12318
36. Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LFA. The

management of osteoradionecrosis of the jaws - A review. *Surgeon*. 2015;13(2):101-109. doi:10.1016/j.surge.2014.07.003
37. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. *Br J Oral Maxillofac Surg*. 2008;46(8):653-660. doi:10.1016/j.bjoms.2008.04.006
38. Tchanque-Fossuo CN, Monson LA, Farberg AS, et al. Dose-response effect of human equivalent radiation in the murine mandible: Part I. A histomorphometric assessment. *Plast Reconstr Surg*. 2011;128(1):114-121. doi:10.1097/PRS.0b013e31821741d4
39. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg*. 1983;41(6):351-357. doi:10.1016/S0278-2391(83)80005-6
40. Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis of the mandible. *Oral Oncol*. 2010;46(11):795-801. doi:10.1016/j.oraloncology.2010.08.007
41. Madrid C, Abarca M, Bouferrache K. Osteoradionecrosis: An update. *Oral Oncol*. 2010;46(6):471-474. doi:10.1016/j.oraloncology.2010.03.017
42. Oh HK, Chambers MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the Mandible: Treatment Outcomes and Factors Influencing the Progress of Osteoradionecrosis. *J Oral Maxillofac Surg*. 2009;67(7):1378-1386. doi:10.1016/j.joms.2009.02.008
43. Dieleman FJ, Meijer GJ, Merkx MAW. Does hyperbaric oxygen therapy play a role in the management of osteoradionecrosis? A survey of Dutch oral and maxillofacial surgeons. *Int J Oral Maxillofac Surg*. 2021;50(2):273-276. doi:10.1016/j.ijom.2020.06.014
44. Nassab PF. Understanding hyperbaric oxygen therapy and its role in the upper extremity. *J Hand Surg Am*. 2011;36(3):529-531. doi:10.1016/j.jhsa.2010.12.001
45. Choudhury R. Hypoxia and hyperbaric oxygen therapy: A review. *Int J Gen Med*. 2018;11:431-442. doi:10.2147/IJGM.S172460
46. Sen S, Sen S. Therapeutic effects of hyperbaric oxygen: Integrated review. *Med Gas Res*. 2021;11(1):30-33. doi:10.4103/2045-9912.310057
47. Wise GE, King GJ. Mechanisms of tooth eruption and orthodontic tooth movement. *J Dent Res*. 2008;87(5):414-434. doi:10.1177/154405910808700509
48. Fosen KM, Thom SR. Hyperbaric oxygen, vasculogenic stem cells, and wound healing. *Antioxidants Redox Signal*. 2014;21(11):1634-1647. doi:10.1089/ars.2014.5940
49. Thom SR. Hyperbaric oxygen: Its mechanisms and efficacy. *Plast Reconstr Surg*. 2011;127(SUPPL. 1 S):1-16. doi:10.1097/PRS.0b013e3181fbe2bf
50. Williams WB, O'Ryan F. Management of Medication-Related Osteonecrosis of the Jaw. *Oral Maxillofac Surg Clin North Am*. 2015;27(4):517-525. doi:10.1016/j.coms.2015.06.007