Article published online: 2023-07-12

Effectiveness of Hyperbaric Oxygen Therapy in the Management of Osteoradionecrosis of the Jaw: A Systematic Review

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J Health Allied Sci[NU]

Abstract

Osteoradionecrosis (ORN) of the jaws is the most dangerous long-term side effect of head and neck radiation therapy that can significantly affect the quality of life of the patients. In ORN of the jaw, the bone within the radiation field becomes devitalized and gets exposed via the overlying skin or mucosa, which remains unhealed. Hyperbaric oxygen therapy (HBOT) is used as an adjunctive therapy along with surgical debridement for the management of ORN of the jaws. HBOT promotes angiogenesis, neovascularization, fibroblast and osteoblast proliferation, and collagen production. However, the benefit of HBOT in improving the healing of tissues in patients with ORN remains controversial because of low evidence. The present systematic review aimed to compare the available data on the efficacy of HBOT on the healing of ORN of the jaw. Databases like PubMed, Scopus, Cochrane, Science Direct, Lilac, and Web of Science were searched without any date filter to obtain the relevant articles. A total of six articles met the eligibility criteria and were further processed for data extraction. Two retrospective studies observed that HBOT combined with surgical debridement promoted wound healing in patients with early stages of ORN of the jaws. Similarly, a prospective study reported that prophylactic HBOT reduced the risk of the development of ORN of the jaws following surgery to irradiated jaws. In contrast, three randomized controlled trials (RCTs) reported that HBOT did not improve the healing outcome of patients with advanced lesions of ORN of the jaws. Based on the scope of this review, we concluded that the routine use of HBOT for the prevention or management of ORN of the jaws is not recommended. Adjunctive HBOT may be considered in patients who have failed conservative therapy and subsequent surgical resection and are regarded to be at high risk.

Keywords
- radiation therapy
- osteoradionecrosis
- mandible
- hyperbaric oxygen therapy
- wound healing

DOI https://doi.org/10.1055/s-0043-1770981.
ISSN 2582-4287.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Radiotherapy is crucial for the management of head and neck squamous cell carcinoma as it results in enhanced tumor control and increased survival rates.[1] Despite recent advancements in this field such as photon therapy, intensity-modulated radiotherapy, volumetric-modulated arc therapy, stereotactic body radiotherapy, and adaptive radiotherapy, patients often develop several radiation-associated toxicities like oral mucositis, infections, xerostomia, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis (ORN).[2] ORN of the jaws is the most dangerous long-term side effect of head and neck radiation therapy that can significantly affect the quality of life of the patients.[3] In ORN of the jaw, the bone within the radiation field becomes devitalized and gets exposed via the overlying skin or mucosa, which remains unhealed.[1]

The global prevalence of ORN ranges from 0.4 to 56%.[4] ORN commonly affects the mandible more than the maxilla; this could be attributed to the relative hypovascular nature and higher bone density of the mandible.[4] Clinically, ORN manifests typically as an area of exposed bone or a fistula that probes to a bone.[1] Mobility of teeth, spontaneous exfoliation of teeth, poor oral hygiene, and food impaction within the exposed bone can also be seen. Patients may exhibit sensory neurological symptoms like dysesthesia, anesthesia along the nerve's distribution, trismus, neuropathic pain, as well as other symptoms like secondary infection with chronic pus drainage, draining extraoral fistulas, or even pathological jaw fracture.[5]

Several theories of etiopathogenesis of ORN have been put forth. A landmark study by Marx[6] provided a novel explanation for development of ORN in the absence of trauma (extraction). He postulated that development of ORN was linked to radiation-induced endarteritis resulting in hypoxia, hypovascularity, and hypocellularity. This idea served as the foundation for the application of hyperbaric oxygen therapy (HBOT) in the treatment of ORN.[7]

HBOT is used as adjunctive therapy along with surgical debridement for the management of ORN of the jaws.[8] In irradiated tissues, it has been hypothesized that HBOT promotes angiogenesis, neovascularization, fibroblast and osteoblast proliferation, and collagen production.[9] However, the benefit of HBOT in improving the healing of tissues in patients with ORN remains controversial because of low evidence.[10] Hence, there is a need to investigate the clinical effects of HBOT on the healing efficacy in ORN patents. The present systematic review aimed to compare the available data on the efficacy of HBOT on the healing of ORN of the jaw.

Materials and Methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The review was registered in the PROSPERO database (the International Prospective Register of Systematic Reviews hosted by the National Institute of Health Research, University of York, Centre for Reviews and Dissemination) with the identification number CRD42023392783. The PICO (population, intervention, comparative intervention, outcomes) component framework was used to formulate a focused research question as follows: In patients with ORN of the jaws, what is the effect of HBOT on healing outcomes compared to conventional therapy?

Two authors (RN and RM) performed an extensive literature search to evaluate the efficacy of HBOT in improving the healing outcome of patients with ORN of the jaw. Online electronic databases like PubMed, Scopus, Cochrane, Lilac, ScienceDirect, and Web of Science were searched from the earliest available data till October 31, 2022. A combination of appropriate keywords and Medical Subject Heading (MeSH) terms like "hyperbaric oxygen therapy," "HBOT," "osteoradionecrosis," and "jaw" was used. A hand search was also done to obtain additional articles. In case of unpublished articles, the authors were contacted. An extensive manual search for relevant articles was also performed to ensure a thorough screening process. A detailed search strategy is illustrated in ►**Fig. 1**.

Randomized controlled trials (RCTs), case-control studies, and cohort studies comparing the healing outcomes with and/or without HBOT in the management of ORN of the jaw were included in the review. Studies conducted on adults above the age of 18 years with no gender or date restriction were included. Articles using any other adjunct therapy to yield better treatment outcomes for ORN of the jaw were excluded. Articles assessing the treatment outcome of HBOT as a secondary outcome were also excluded.

All the searched data were imported into an Excel spreadsheet (MS Excel 2020). The titles and abstracts of the included studies were screened from the above-mentioned databases independently by two reviewers (RN and RM). The articles were selected for full-text reading if the search keywords were present in the title and the abstract. After selection, two reviewers read the full-text articles in detail (RN and RM). The articles that fulfilled all selection criteria were processed for data extraction. Two reviewers (RN and RM) searched the reference lists of all selected studies for additional relevant articles. Disagreements between the two reviewers were resolved by discussion. If a conflict persisted, the judgment of a third reviewer (SK) was considered decisive.

Two reviewers (RN and RM) used a standardized form to extract the relevant data. Any disagreement was resolved by discussion between the authors. Information curated for data extraction included author/year of publication, patient characteristics like mean age, gender, number of patients, study design, HBO regimen, application of HBO as therapy or prophylaxis, study results, and conclusion. Disagreements between individual judgments in data extraction were resolved by taking the opinion of the third reviewer (SK). The extracted data were recorded using an Excel spreadsheet (MS Excel 2020).

The risk-of-bias assessment was evaluated independently by two reviewers (SM and RM) and then discussed with a third reviewer (SK) to resolve any disagreements and provide a final judgment. For RCTs, version 2 of the Cochrane risk-of-

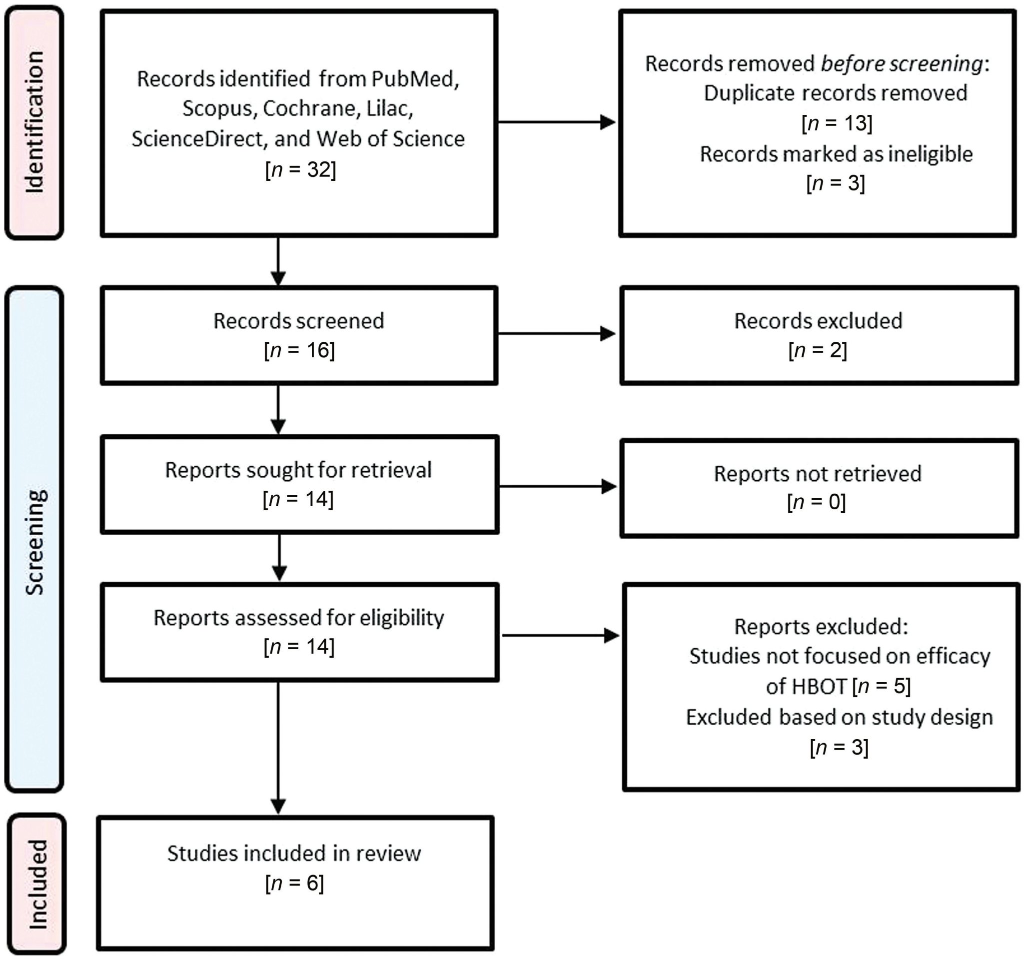

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flowchart.

bias tool for randomized trials (RoB 2) was used.[11] The Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E) tool was applied to assess the risk of bias among the included observational studies.[12] The level of evidence was assigned according to the Agency for Healthcare Research and Quality (AHRQ) 2016 classification of the level of evidence.[13]

Results

The PubMed, Scopus, Cochrane, Lilac, ScienceDirect, and Web of Science databases using the predetermined MeSH terms and hand-searched articles yielded a total of 32 articles, of which 13 were duplicates. Sixteen titles and abstracts were identified as the related subjects of inclusion criteria. After analyzing 16 abstracts, 12 articles were finalized for full article screening. Finally, six articles were included in the review based on the eligibility criteria.[14–19] PRISMA flowchart (►**Fig. 1**) summarizes the selection of included studies.[20]

The total number of participants in the included studies was 386. The sample size varied from 33 to 100. Two studies were retrospective, one study was prospective, and three were RCTs. Among the included studies, 62.18% of the participants were males ($n = 240$). All the studies included adult participants, with the mean age ranging from 54 to 61 years. Among the six included studies, one study each was conducted in Thailand, Paris, Denmark, India, and Australia. The study by Forner et al was a multicentric study conducted in Denmark, Sweden, the United Kingdom, and the Netherlands.[19] Demographic details have been tabulated in ►**Table 1**.

Recovery from Osteoradionecrosis

Six papers analyzed the effectiveness of HBOT in the management of ORN of the jaws. In their trial, Annane et al deployed HBOT and placebo in patients with ORN of jaws, and observed that 19.3% of patients recovered from ORN in the HBOT arm, while 32.4% of the patients recovered in the placebo arm.[16] Shaw et al reported recovery of 7% of patients in the HBOT arm as well as the non-HBOT arm.[17] In a trial by Forner et al, healing from ORN was observed in 51% of patients treated with surgery alone, and 70% of patients treated with surgery along with HBOT.[19] In their retrospective study, Vudiniabola et al found that 28/29 patients showed complete healing of ORN with prophylactic HBOT.[15] Gupta et al observed that 48% of patients with ORN of jaws showed complete healing of wounds, 18% of patients had marked healing, 24% of patients had slight healing, and 9% of patients had no change in healing with therapeutic HBOT.[18] Jenwitheesuk et al conducted a retrospective study on patients with ORN and found that HBOT had a significant role in improving wound healing in patients with stage 1 and 2 ORN.[14] A detailed description of included studies has been tabulated in ►**Table 2**.

Secondary Outcomes

Different secondary outcomes were assessed among the included studies. In their trial, Annane et al reported that among the 68 patients, 20 patients in the HBOT arm and 22 patients in the placebo arm underwent surgery. The subsequent recovery rates were 85% in the HBOT arm and 77.3% in the placebo arm after the first surgery, and 85 and 90.9% in the HBOT and placebo arms, respectively.[16] Shaw et al observed that no new ORN lesions developed at 6 and 12 months of follow-up.[17] In a trial by Forner et al, the surgery with HBOT appeared to be more beneficial for managing xerostomia, unstimulated whole saliva flow rates, and dysphagia.[19] In their retrospective study, Vudiniabola et al reported that 68% of patients found HBOT to be a bearable experience, 26% found it pleasurable, and 5% felt it was unbearable.[15] Gupta et al observed that 70% of cases had a significant reduction in pain, 62% of cases had improved jaw opening, 41% of cases showed improvement in the ability to talk, and 71% of cases showed improvement in dry mouth.[18]

Synthesis of Result

Although data were extracted systematically for this review, a meta-analysis was not possible owing to the heterogeneity and inconsistency of data of the included studies.

Risk of Bias and Quality Assessment

Among the RCTs, one study had a low risk of bias, while two studies had a high risk of bias (►**Fig. 2**). All three observational studies had a low risk of bias (►**Fig. 3**). Three studies were assigned a level II evidence, as they were RCTs. The other three studies were observational retrospective studies and were assigned level IV evidence.

Discussion

ORN significantly hampers the quality of life, particularly in the advanced stages of the disease.[21] Males older than 55 years with a history of tobacco and alcohol consumption are at a higher risk of developing ORN of the jaw.[1] Risk factors associated with ORN can be broadly categorized as tumor-related factors like the extent of the tumor, proximity of the tumor to the bone, bone invasion, and the need for preradiation bone resection; treatment-related factors like radiation dose and frequency; and host factors like the presence of a preexisting dental disease, the need for a preirradiation surgical procedure, and poor oral hygiene.[2]

ORN complicates rehabilitation procedures like free tissue grafts in head and neck cancer patients and may cause unfavorable results. Physicians and surgeons must consider ORN as a potential complication while performing tooth extractions or surgical procedures in irradiated patients.[22] Several studies have demonstrated that HBOT plays a

Table 1 Demographic details of included studies (original table created by the reviewers)

Sl no.	Study	Place	Type of study	Level of evidence	No. of patients (*n*)	HBO	Non-HBO	Male	Female	Age (mean)
1	Annane et al[16]	Paris	RCT	2	68	31	37	59	9	54 y
2	Shaw et al[17]	Denmark	RCT	2	100	47	53	28	72	58.2 y
3	Forner et al[19]	Denmark, Sweden, UK, the Netherlands	Multicentric RCT	2	65	30	35	55	10	61 y
4	Vudiniabola et al[15]	Australia	Prospective	4	36	29	7	26	10	54.5 y
5	Gupta et al[18]	India	Retrospective	4	33	33	0	26	7	59.8 y
6	Jenwitheesuk et al[14]	Thailand	Retrospective	4	84	84	0	46	38	58.78 y

Abbreviation: HBO, hyperbaric oxygen; RCT, randomized controlled trial.

Table 2 Description of included studies (Original table created by the reviewers)

Sl no	Study	Type of use	HBO regimen	Primary outcome	Secondary outcome	Conclusion
1	Annane et al[16]	Preventive and therapeutic	30 preoperative HBO exposures and additional 10 postoperative HBO exposures at 2.4 atmosphere for 90 min	19.3% of patients recovered in the HBOT arm, and 32.4% of patients recovered in the placebo arm	The recovery rate was 85% in the HBOT arm and 77.3% in the placebo arm after a first surgery. After a second surgery, the recovery rates were 85 and 90.9% in the HBOT and placebo arms, respectively	Patients with overt mandibular ORN did not benefit from HBOT
2	Shaw et al[17]	Preventive	30 daily dives at 2.4 atmosphere for 80–90 min (20 presurgery and 10 postsurgery)	Healing seen in 7% patients in the HBOT arm and 7% patients on the non-HBOT arm	No new ORN developed between 6 and 12 mo	Patients with overt mandibular ORN did not benefit from HBOT
3	Forner et al[19]	Therapeutic	30 pre- and 10 postoperative HBOT exposures at 243 kPa for 90 min	Healing seen in 51% patients treated with surgery alone and in 70% patients treated with surgery + HBOT	The surgery + HBOT arm appeared to be more beneficial for xerostomia, unstimulated whole saliva flow rates, and dysphagia	HBOT did not significantly improve the healing outcome of ORN after surgical removal of necrotic bone as compared to standard care
4	Vudiniabola et al[19]	Preventive	5 HBO with <30 dives, 3 HBO with >30 dives, and 21 HBO with 30 dives	HBOT group ($n = 29$) fully healed: 28/29; ORN: 1/29 Control group ($n = 7$) fully healed: 6/7; ORN: 1/7	68% participants felt HBOT was a bearable experience, 26% found it pleasurable, and 5% felt it was unbearable	Prophylactic HBOT reduced the risk of ORN developing following surgery to irradiated jaws
5	Gupta et al[18]	Therapeutic	2.4 ata, for 90 min once a day for up to 30 sessions	48% cases showed complete healing of wound, 18% cases had marked healing, 24% cases had slight healing, and 9% cases had no change in healing	70% cases had significant reduction in pain, 62% cases had improved jaw opening, and 41 and 71% cases showed improvement in the ability to talk and mouth dryness, respectively	HBOT should be one of the primary treatment modalities for mandibular ORN to improve the quality of life in these patients
6	Jenwitheesuk et al[14]	Adjunctive	Daily 20 HBO dives before and 10 after the surgery at 2.4 atmosphere for 90 min	Stage 1: less HBOT dives (small lesion) Stage 2: more dives are needed along with bone resection Stage 3: less dives needed as bone debridement or bone resection is already done	Not assessed	HBOT had a significant role in improving wound healing of ORN patients in stages 1 and 2

Abbreviation: ata, atmosphere absolute; HBO, hyperbaric oxygen; HBOT, hyperbaric oxygen therapy; ORN, osteoradionecrosis; RCT, randomized controlled trial.

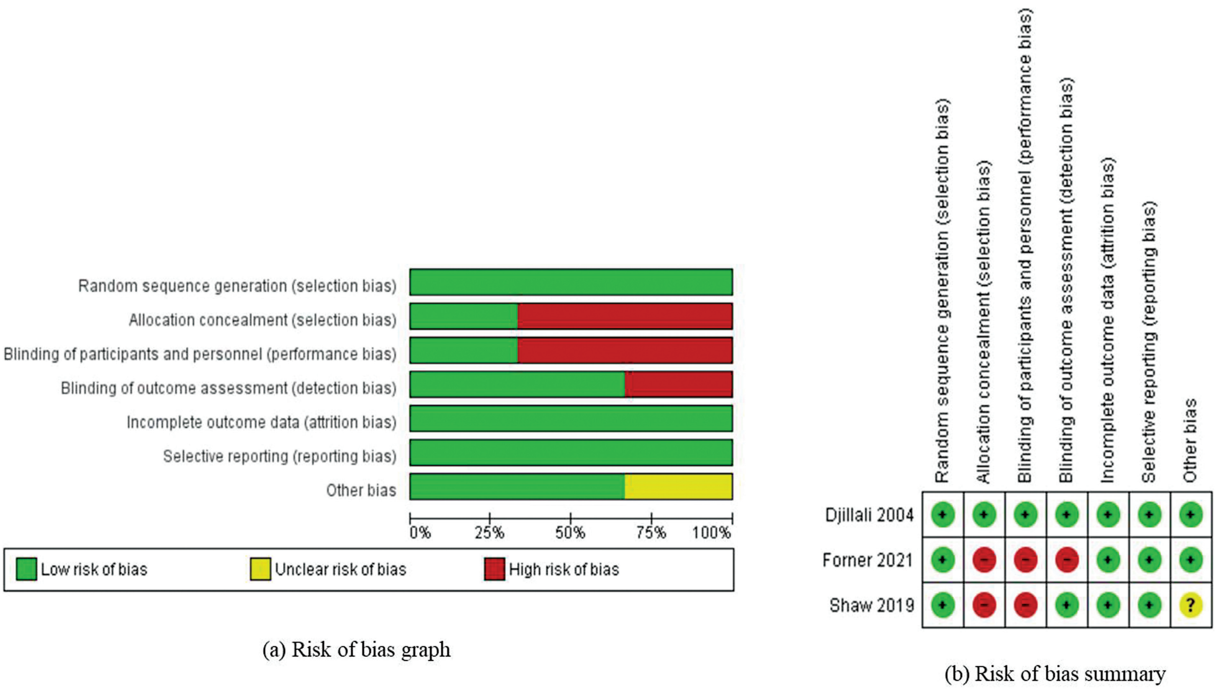

Fig. 2 (**a**, **b**) Risk of Bias 2 (RoB-2) tool for randomized controlled trials.

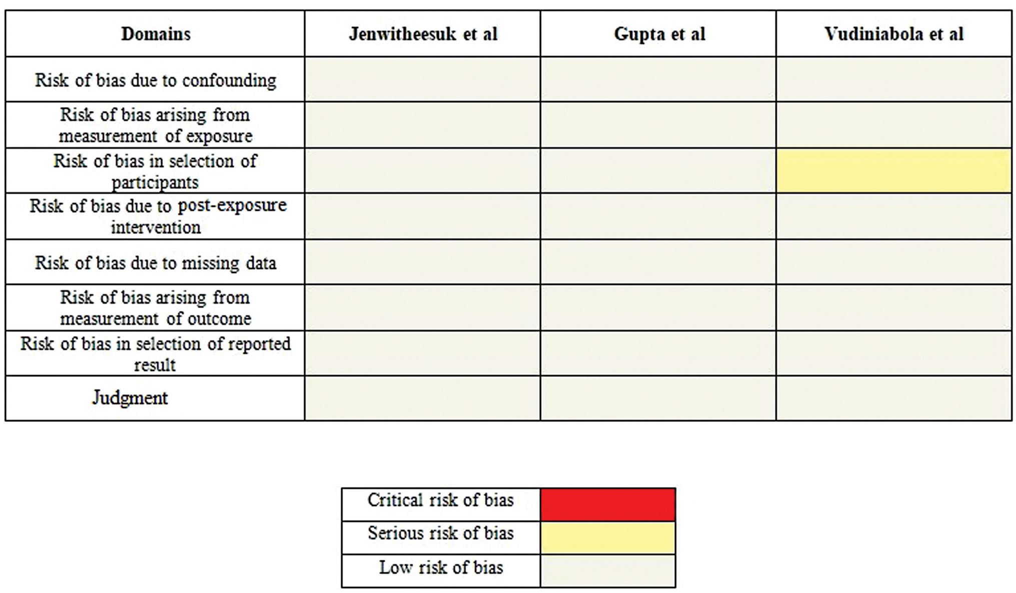

Fig. 3 Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E) tool for observational studies.

significant role in the management of ORN of the jaws.[14,15,18] An international consensus on the HBOT protocol recommended 30 dives before and 10 dives after the surgery at 2.4 atm pressure, for 90 minutes.[23]

Nonirradiated wounds have a focal area of tissue injury surrounded by normal tissue perfusion, resulting in a sharp oxygen gradient across the wound. This gradient attracts macrophages to the lesional site and enhances macrophage-derived angiogenesis and growth factors, which promote capillary budding and collagen production in wounds.[24] However, in wounds with radiation tissue injury, only a modest oxygen gradient is created, resulting in decreased fibroplasia, angiogenesis, and poor wound healing. It has been postulated that HBOT promotes wound healing by raising local tissue oxygen tension, which enhances collagen synthesis, angiogenesis, bone regeneration, and oral tissue re-epithelization to combat hypoxia, hypocellularity, and hypovascularity caused by radiotherapy.[25] Researchers and clinicians have utilized HBOT as a therapeutic/prophylactic monotherapy or adjunctive therapy before dental extractions to manage ORN in irradiated patients.[14–19]

In our systematic review, two retrospective studies with a smaller sample size observed that HBOT combined with surgical debridement promoted wound healing in patients with early stages of ORN of the jaws.[14,18] Similarly, a prospective study reported that prophylactic HBOT reduced the risk of the development of ORN of the jaws following surgery to irradiated jaws.[15] These findings were in accordance with a systematic review that concluded based on weak evidence that prophylactic HBOT was effective in reducing the risk of developing ORN of the jaws after postradiation extractions. However, these studies lacked control groups, and the definitions of ORN and HBOT regimens used in these studies varied extensively.[25]

In contrast, the three RCTs included in the review reported that HBOT did not improve the healing outcome of patients with advanced lesions of ORN of the jaws.[16,17,19] This was in accordance with the review by Sultan et al, who did not recommend the routine use of HBOT for the management of ORN of the jaws.[25] Since RCTs rank higher in the level of evidence and the observational studies had methodological flaws, we conclude that HBOT is ineffective.

Evaluation of secondary outcomes showed a beneficial effect of adjunctive HBOT on various parameters like radiation-induced xerostomia, salivary flow rate, dysphagia, postsurgical recovery, and the absence of new ORN lesions on follow-up.[15–19] A study by Harding et al reported that HBOT has the potential to relieve radiation-induced hyposalivation, thereby improving the quality of life of the patients.[26]

Limitations

Although rigorous inclusion and exclusion criteria were followed, this systematic review has a few limitations. First, the majority of studies were single-center studies with vastly different follow-up lengths and limited sample sizes, frequently with an uneven distribution of patients in the study arms. The number of included studies is too small to draw conclusive evidence regarding the effectiveness of HBOT in improving the healing outcome of patients with ORN of the jaws. Second, critical information regarding the number of teeth extracted, the surgical procedure performed, the amount of baseline bone injury, and the specific treatment regimen provided to the patients in the non-HBOT arms was consistently inadequate. Third, several studies did not mention the radiation dose delivered to the HBOT and non-HBOT groups in detail. Finally, quantitative synthesis of the result was not possible to due heterogeneity and inconsistency of data of the included studies. Given the lack of conclusive data, the high expense of treatment, and the limited number of HBOT facilities, the utility of HBOT in the therapeutic setting remains debatable.

Future Research Directions/Recommendations

In the future, large multicentric studies with a larger sample size, uniform methodology, and a longer follow-up time should be encouraged to arrive at conclusive evidence. The aim should be to develop a standardized treatment strategy for delivering HBOT to patients based on the stage and severity of ORN. A personalized HBOT regimen needs to be formulated on a case-to-case basis, taking all clinical and radiographic parameters into account. Future research must focus on the comparison of HBOT with the existing conventional nonsurgical treatment modalities for the management of ORN of the jaws. The HBOT regimen can be tried out in refractory cases of ORN that fail to heal by conventional therapies.

Conclusion

ORN of the jaws is a serious complication of head and neck radiotherapy with a significant implication on the treatment outcome and quality of life of the patient. Based on our review, we conclude that the routine use of HBOT for the prevention or management of ORN of the jaws is not recommended. Adjunctive HBOT may be considered in patients who have failed conservative therapy and subsequent surgical resection and are regarded to be at particularly high risk.

Conflict of Interest
None declared.

References

1 Singh A, Huryn JM, Kronstadt KL, Yom SK, Randazzo JR, Estilo CL. Osteoradionecrosis of the jaw: a mini review. Front Oral Health 2022;3:980786
2 Sroussi HY, Epstein JB, Bensadoun RJ, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med 2017;6(12):2918–2931
3 Suryawanshi AT, Santhosh Kumar SN, Dolas RS, Khindria R, Pawar V, Singh M. Maxillofacial osteoradionecrosis. Journal of Dental Research and Review. 2014;1(01):42
4 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(01):22–30
5 Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg 2008;46(08):653–660
6 Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg 1983 May;41(05):283–288
7 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;18:13
8 Ceponis P, Keilman C, Guerry C, Freiberger JJ. Hyperbaric oxygen therapy and osteonecrosis. Oral Dis 2017;23(02):141–151
9 Ngeow WC, Tan CC, Goh YC, Deliberador TM, Cheah CW. A narrative review on means to promote oxygenation and angiogenesis in oral wound healing. Bioengineering (Basel) 2022;9(11):636
10 Costa DA, Costa TP, Netto EC, et al. New perspectives on the conservative management of osteoradionecrosis of the mandible: a literature review. Head Neck 2016;38(11):1708–1716
11 Risk of Bias 2 (RoB 2) tool. Accessed March 2, 2023 at: https://methods.cochrane.org/risk-bias-2
12 Bero L, Chartres N, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. Syst Rev 2018;7(01):242

13 Agency for Healthcare Research and Quality Grading the Strength of a Body of Evidence when Comparing Medical Interventions. Accessed April 20, 2023 at: https://effectivehealthcare.ahrq.gov/products/methods-guidance-grading-strength/methods
14 Jenwitheesuk K, Mahakkanukrauh A, Punjaruk W, et al. Efficacy of adjunctive hyperbaric oxygen therapy in osteoradionecrosis. Biores Open Access 2018;7(01):145–149
15 Vudiniabola S, Pirone C, Williamson J, Goss AN. Hyperbaric oxygen in the prevention of osteoradionecrosis of the jaws. Aust Dent J 1999;44(04):243–247
16 Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. J Clin Oncol 2004;22(24):4893–4900
17 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(03):530–539
18 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
19 Forner LE, Dieleman FJ, Shaw RJ, et al. Hyperbaric oxygen treatment of mandibular osteoradionecrosis: combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1. Radiother Oncol 2022;166:137–144
20 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71):n71
21 Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 2018;69:177–187
22 Devi S, Singh N. Dental care during and after radiotherapy in head and neck cancer. Natl J Maxillofac Surg 2014;5(02):117–125
23 Shah J. Hyperbaric oxygen therapy. J Am Col Certif Wound Spec 2010;2(01):9–13
24 Schultz GS, Chin GA, Moldawer L, Diegelmann RF. Principles of wound healing. In: Fitridge R, Thompson M, eds. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists. Adelaide, Australia: University of Adelaide Press; 2011
25 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(03):343–350
26 Harding SA, Hodder SC, Courtney DJ, Bryson PJ. Impact of perioperative hyperbaric oxygen therapy on the quality of life of maxillofacial patients who undergo surgery in irradiated fields. Int J Oral Maxillofac Surg 2008;37(07):617–624

