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ADJUNCTIVE HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF OSTEORADIONECROSIS OF THE JAWS IN IRRADIATED HEAD AND NECK CANCER PATIENTS - A SYSTEMATIC REVIEW AND META-ANALYSIS.

Dental Science

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ABSTRACT

Worldwide, head and neck cancer accounts for 3,30,000 deaths annually. Malignant tumors in the head and neck region are treated by surgery with chemotherapy and or radiotherapy. Radiationresults in acute or late injury to surrounding normal tissue known as Osteoradionecrosis. A literature search of major databases was performed for the identification of studies on the use of adjunctive hyperbaric oxygen therapy in treatment of osteoradionecrosis of the jaws. Six publications including 158 patients were considered. This meta-analysis is consistent with the results of studies documented in literature and confirms its modest usefulness as an option in this patient population, with a disease cure-rate of about 46.35% ((CI: 22.74- 70.87) and no new adverse effects.

KEYWORDS

adjunctive, hyperbaric oxygen therapy, head and neck cancer, radiation, osteoradionecrosis of jaw.

INTRODUCTION

Radiotherapy is used for treatment of head and neck cancer as primary therapy, adjuvant to surgery, with concurrent chemotherapy or as palliative treatment for unresectable head and neck malignancies[1]. It targets all cells; malignant or normal tissue cells with a high turnover rate. One of its most severe complications is Osteoradionecrosis (ORN)[(1)].In 1983, Marxdefined ORN as 'an area >1 cm of exposed bone in a field of irradiation that failed to show any evidence of healing for at least 6 months'. He reported that pathophysiologically, ORN was represented by hypoxia, hypovascularization and hypocellularity (3-H concept)[(2)]. According to Delanian and Lefaix's 'fibroatrophic theory', fibroblast activation and dysregulation resulted in radiation-induced fibrosis of soft and hard tissue[(3)].

ORN can occur spontaneously due to periodontal, apical diseases, trauma induced by dentures, after surgery or tooth extraction(6). When the dose exceeds 50 to 60 Gy[(10)] or when the previously irradiated region undergoes trauma (e.g. tooth removal). In our meta-analysis the included studies have taken into account classifications according to Robert Marx and Notani et al. [(3)]

Head and neck irradiated patients show prevalence ranges from 10-15%. [(4)] The goals of ORN treatment are to restore vascularization, allow the wound healing process to occur and thereafter, maintain normal tissue homeostasis. Its conservative management consists of antibiotics, antiseptics and small sequestrum removal. [(4)]Patients with pathologic fracture, an oro-cutaneous fistula or full thickness devitalized bone require surgical approaches such as resection, reconstruction with bone graft and fistulectomy.[(12)]

ORN was recognized as an indication for Hyperbaric Oxygen Therapy (HBOT) use in delayed radiation injury (soft tissue and bony necrosis) in the 2003 Undersea Hyperbaric Medical Society Committee Report.[(9)]It consists of inhaling 100% oxygen at an elevated pressure (above 1.5 atmospheres).

HBOT assists in the repair of radiation induced damage; improves oxygenation of tissue, promotes neovascularization and help eradicate bacteria in damaged tissue.[(6)]

The Marx's protocol for ORN treatment consists of a 90-minute session at 2.4 atmospheres, once a day for 30 days before the surgery and 10 days after the surgery.[(6)]The interval between radiation therapy and the onset of ORN varies between 4 months and as much as 20 years,with a peak incidence at 2–4 years and a remaining lifelong risk, albeit to a lesser degree.[(8)]

This meta-analysis aims to pool these studies and analyze the effectiveness of this modality as an adjunct to surgery and provide a road-map for future research of its use.

METHODS

Protocol

This Systematic Review and Meta-analysis (SRMA) was done using the Preferred Reporting items for systematic reviews and meta-analysis (PRISMA).

Literature Search Strategy

Databases like PUBMED, GOOGLE SCHOLAR, SCOPUS, COCHRANE, MEDLINE and EMBASE were searched for articles published between 2000 to 2017 with keywords mentioned in the abstract.

Eligibility Criteria

The included studies were randomized controlled trials (RCT) and retrospective cohort and case control studies. Full-text articles published in English and relevant articles mentioned in reference lists of selected articles were selected. Publications in other languages or as abstracts were excluded.

Study Selection

Articles assessing the adjunctive use of HBOT in treatment of ORN were considered. All retrieved articles were evaluated by two reviewers independently. A conflict between the reviewers was resolved by consensus. After excluding the non-eligible articles, they were screened according to their titles and abstracts. Full-text articles were assessed and the articles which didn't meet the inclusion criteria were excluded.

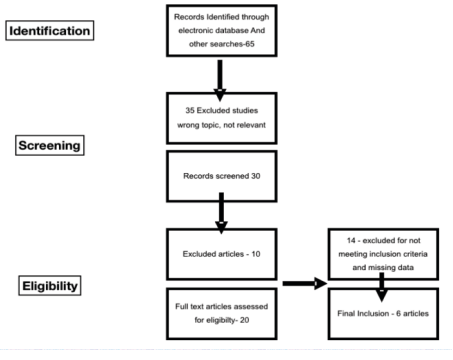

Fig.1 - PRISMA Flow Diagram

Type of intervention

In the RCTs included, the intervention group received adjunctive hyperbaric oxygen therapy along with surgery while the control group received placebo.

Risk of bias assessment

The Cochrane Collaboration's Tool was used for assessing the risk of bias for RCTs and the Newcastle-Ottawa Scale for Quality Assessment forRetrospective case-control and cohort studies. The status of bias of each included trial was assessed both at the study and outcome level.

Table 1: Cochrane Collaboration's Tool

Bias	Author's Judgement	Support for Judgement
Random Sequence Generation (selection bias)	Unclear Risk	It is mentioned that the patients were divided randomly into two groups. However the distribution of the sample size was unequal in the groups
Allocation Concealment (Selection Bias)	Low Risk	Allocation done by the pharmacist
Blinding of participants & personel (Performance Bias)	High risk	Double-blind study, however the outcome can be influenced by lack of blinding
Blinding of outcome assessment (Detection Bias)	Unclear Risk	Not mentioned
Incomplete outcome data (Attrition Bias)	Unclear Risk	Not mentioned
Selective Reporting (Reporting Bias)	Unclear Risk	Not mentioned
Other Bias	Unclear Risk	Not mentioned

Table 2: Newcastle-Ottawa Scale for Quality Assessment for Retrospective case-control and cohort studies

Overall Risk of Bias for Retrospective Cohort and Case control Studies

Study	Selection	Comparability	Exposure/ Outcome	Total Score
Dieleman et al	**	-	**	4/9
Dsouza et al	***	-	***	6/9
Gavriel et al	**	-	***	5/9
Gupta et al	**	-	***	5/9
Bui et al	***	*	***	6/9

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Data extraction and analysis

Data was extracted from the selected 6 articles using Microsoft Excel and transferred to RevMan 5.3 for meta-analysis. Heterogeneity between studies was assessed using the I^2 statistic. Heterogeneity was considered substantial if $I^2$was greater than 50% and a random effects model applied; otherwise, a fixed effects model was used for the analysis. The pooled data for each outcome were reported as Response Rate (RR). The publication bias of the articles was assessed using funnel plot.

RESULTS

Study selection

65 articles were assessed for eligibility. From which 20 full texts were assessed for eligibility. Only 6 were selected for the final review (Fig 1).

Study characteristics

Methods

All six studies selected were RCTs, Retrospective studies published in English between 2004 and 2016. The studies were conducted in India, France, USA, UK, Netherlands and Israel.

Participants

The 6 studies included 158 participants. They received HBOT as an adjunct to surgery for the treatment of ORN.The most common sites of metastatic involvement were oropharynx, larynx, parotid glands, tongue, maxillary sinus, alveolar ridge, thyroid gland. Average amount of radiation therapy that all the patients in the included studies received was 50-70 Gy. Standard inclusion and exclusion criteria were mentioned in all studies. Average time period that elapsed between cessation of radiation therapy and development of Osteoradionecrosis was 1 year.

Outcome

All the studies mentioned the outcome in terms of Resolution of ORN clinically and, or radiologically, commonly expressed as cure or response rate.

Risk of Bias Assessment

A funnel plot was used to assess the presence of publication bias between the included studies and illustrated a symmetrical spread of the studies with regards to the standard error. This symmetrical distribution showed the presence of low publication bias and also shows high reliability.

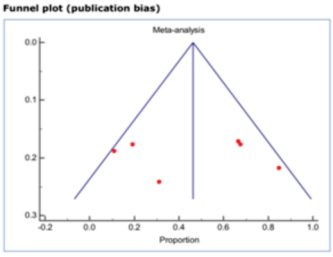

Fig. 2 - Funnel plot

Results of Individual Studies (Fig.3)

The study by Dieleman et al showed a proportion increase of response rate as 11%.The study by Dsouza et al -31.25% proportion increase in response rate. The study by Gavriel et al - 85% proportion increase in response rate. The study by Annane et al- 19.35 % proportion increase in response rate. The study by Gupta et al - 66.66% proportion increase in response rate. The study by Bui et al - 67.72 % proportion increase in response rate. The pooled response rate of meta-analysis in all the studies was 46.35% (95% CI- 22.74 to 70.87).

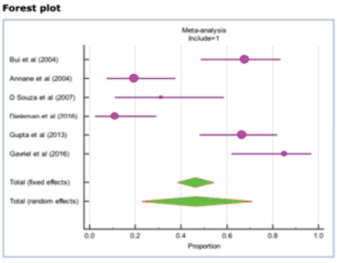

Fig. 3 - Pooled Response Rate of included Studies

Analysis of Heterogeneity

Using the MedCalc statistical software, The I^2 was 90.62%, which was substantial and random effect model was considered for the analysis ($p < 0.00001$). The funnel plot was symmetrical and showed there was no significant publication bias.

DISCUSSION

Robert Marxcompared the effect of HBOT in irradiated mandibles that required dental extraction with that in a control group and found a decrease in the incidence of ORN from 29.9% in the control group to 5.4% in the HBOT group. These findings paved the way for the clinical use of HBOT in irradiated head and neck tissue.

Many cases of mild ORN heal either on their own or with limited surgical debridement. There are few options for treatment of complex or persistent cases other than complete surgical resection or multimodal therapy where HBOT is combined with surgical extirpation of necrotic bone.

Marx's staging systemis based on the use of and response to HBOT. The advantages of this protocol include selection of patients who are able to respond to less aggressive treatments, use of minimal levels of HBOT, resolution of the disease and preparation of patients' tissues for reconstruction without further HBOT(7).

In our systematic review and meta-analysis, we have included retrospective studies as adequate follow-up to check its effectiveness

and risk factors were addressed, along with loss of follow-up if any.

In a study by Annane et al, therapy including surgery andHBOT was not uniformly applied in the HBOT group because surgical debridement of devitalized bone was not emphasized.The patients enrolled in this study received HBOT or placebo twice a day, which differs from the 1-session-a-day protocol. The HBO arm showed a poor response rate. Being a multi-center study, there was a deviation from the standard Marx Protocol. The study by D'Souza et alexemplifies the problem of evaluating therapy whenever disease severity and the therapy under evaluation are linked.HBOTwas of little use based on a cure rate of 12.5% compared with 86% in patients not receiving HBOT in 23 cases over 8 years. The significant increase in mortality rate for the hyperbaric groups suggests that these patients had ongoing or recurrent malignancy and that ORN might have been misdiagnosed or become camouflaged instead of an actual diagnosis of malignant recurrence causing exposedbone.

In the study by Dieleman, they showed a beneficial effect of HBOT for the lower ORN stages (I & II). Stage III ORN usually requires a resection of the affected part of the mandible. It is unclear what the added value of HBOT is to the bone in cases of extensive ORN. If the soft tissues surrounding the ORN region are in a poor state, HBOT could be recommended to promote revascularization and aid in wound healing after free flap reconstruction. Surgery is mandated in such cases.

In the study by Gavriel et al, the efficacy of HBOT for maxillary bone ORNJ was supported. They showed a response rate of 85%. However the drawbacks were that their cohort extended over 15 years, making the complete evaluation of patient outcome difficult. Also the previous treatments at other medical centers had failed after which this cohort was selected.

In the study by Gupta et al, the response or the cure rate was 66%, and they concluded that HBOT should be one of the primary treatment modalities for ORNJ along with local wound care, surgery and antibiotics.

In the study by Bui et al, the total response rate was 67%. The study advocated the use of HBOT; however, patients with protracted side effects tended to be less likely to respond well to HBOT even when combined with surgery.

The HBOT protocol was not standardized in all the studies. Deviation from Marx Protocol was observed, despite which HBOT was effective in the treatment of ORN.

CONCLUSION

This meta-analysis is consistent with the results of studies documented in literature and confirms its modest usefulness as an option in the mentioned patient population and no new adverse effects concerns.

Keeping in mind its ill-effects, contra-indications and exorbitant costs, its use can be instilled as an adjunct to promote neo-angiogenesis. There is a need for meticulously-designed randomized controlled trials in the field of hyperbaric medicine, as an adjunctive modality in ORN of the jaws.

Conflicts of interest

None

REFERENCES

1) Nabil, S., &Samman, N. (2011). Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: A systematic review. International Journal of Oral and Maxillofacial Surgery, 40(3), 229–243. https://doi.org/ 10.1016/ j.ijom.2010.10.005
2) Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg. 1983;41 (5):283-8.
3) Dhanda, J., Pasquier, D., Newman, L., & Shaw, R. (2016). Current Concepts in Osteoradionecrosis after Head and Neck Radiotherapy. Clinical Oncology, 28(7), 459–466. https://doi.org/10.1016/j.clon.2016.03.002
4) Gupta, P., Sahni, T., Jadhav, G. K., Manocha, S., Aggarwal, S., &Verma, S. (2013). 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 Journal of Otolaryngology and Head & Neck Surgery, 65(S1), 140–143. https://doi.org/10.1007/s12070-013-0640-z
5) Bui, Q.-C., Lieber, M., Withers, H. R., Corson, K., van Rijnsoever, M., &Elsaleh, H. (2004). The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. International Journal of Radiation Oncology*Biology*Physics, 60(3), 871–878. https://doi.org/10.1016/j.ijrobp.2004.04.019
6) Chouinard, A.-F., Giasson, L., & Fortin, M. (n.d.). Hyperbaric Oxygen Therapy for Head and Neck Irradiated Patients with Special Attention to Oral and Maxillofacial Treatments.
7) Chronopoulos, A., Zarra, T., Ehrenfeld, M., & Otto, S. (2018). Osteoradionecrosis of the jaws: Definition, epidemiology, staging and clinical and radiological findings. A concise review. International Dental Journal, 68(1), 22–30. https://doi.org/10.1111/idj.12318
8) Dieleman, F. J., Phan, T. T. T., van den Hoogen, F. J. A., Kaanders, J. H. A. M., &Merkx, M. A. W. (2017). The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible. International Journal of Oral and Maxillofacial Surgery, 46(4), 428–433. https://doi.org/10.1016/j.ijom.2016.12.004
9) Freiberger, J. J., &Feldmeier, J. J. (2010). Evidence Supporting the Use of Hyperbaric Oxygen in the Treatment of Osteoradionecrosis of the Jaw. Journal of Oral and Maxillofacial Surgery, 68(8), 1903–1906. https://doi.org/10.1016/j.joms.2010.02.001
10) Ohba, S., Yoshimura, H., Kobayashi, J., Ishimaru, K., Matsuda, S., Katase, N., Imamura, Y., Ueno, T., & Sano, K. (2013). The Influence of Radiation Therapy and Hyperbaric Oxygen Therapy on Osteoradionecrosis of the Jaw. Journal of Hard Tissue Biology, 22(1), 147–152. https://doi.org/10.2485/jhtb.22.147
11) D'Souza, J., Goru, J., Goru, S., Brown, J., Vaughan, E. D., & Rogers, S. N. (2007). The influence of hyperbaric oxygen on the outcome of patients treated for osteoradionecrosis: 8 year study. International Journal of Oral and Maxillofacial Surgery, 36(9), 783–787. https://doi.org/10.1016/j.ijom.2007.05.007
12) Gavriel, H., Eviatar, E., & Abu Eta, R. (2017). Hyperbaric oxygen therapy for maxillary bone radiation-induced injury: A 15-year single-center experience: Hyperbaric oxygen therapy for maxillary osteoradionecrosis. Head & Neck, 39(2), 275–278. https://doi.org/10.1002/hed.24577
13) Bui, Q.-C., Lieber, M., Withers, H. R., Corson, K., van Rijnsoever, M., &Elsaleh, H. (2004). The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. International Journal of Radiation Oncology*Biology*Physics, 60(3), 871–878. https://doi.org/10.1016/j.ijrobp.2004.04.019