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RESEARCH ARTICLE

ROLE OF HYPERBARIC OXYGEN THERAPY AS AN ADJUNCT IN IMPROVING OUTCOME OF TREATMENT OF OSTEORADIONECROSIS OF MANDIBLE- A RETROSPECTIVE STUDY

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ABSTRACT

Background: Osteoradionecrosis (ORN) is defined as an area of exposed necrotic bone, in an area previously irradiated, that fails to heal over a period of 3–6 months in the absence of recurrence of tumour. ORN of mandible, though rare, is a serious and dreaded complication of radiotherapy. **Aim:** To study the role of hyperbaric oxygen therapy (HBOT) as an adjunct in improving outcome of treatment of ORN of mandible. **Material and Methods:** A retrospective analysis was done, from 2015-2017, of various head, neck and oral cancer patients who developed ORN and were treated with HBOT at our centre. The subjects underwent 30 sessions of 2.4ATA for 60min, five times a week in a monoplace hyperbaric chamber. The parameters observed, both pre and post HBOT were wound healing, pain relief and overall wellbeing. **Results:** The study included 80 patients with a mean patient age of 53.5yrs. 24 (30%) patients improved with HBOT alone. However, 37(46.25%) patients required sequestrectomy and 19 (23.75%) underwent surgery for resection/flap cover along with HBOT. Further 10-15 sittings of HBOT were given to them post-operatively. **Conclusion:** HBOT alone and as an adjunct to surgery shows encouraging results. Our study corroborates the existing literature on the potential benefit of HBO as a adjunctive treatment of ORN.

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INTRODUCTION

Cancer of head and neck and oral cavity is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of patients having radiotherapy will be long-term survivors. Some will experience late radiation tissue injury developing months or years later. Osteoradionecrosis (ORN) of the mandible is a delayed and one of the most dreaded complications of radiation therapy. ORN is defined as the exposed necrotic bone in an area, previously irradiated, that fails to heal over a period of 3–6 months in absence of recurrence of tumour. Radiotherapy results in tissue hypovascularity, hypocellularity and hypoxia which forms the basis of pathophysiology of ORN. Reported incidence of ORN ranges from 5% to 15% (Adepitan *et al*., 2017). ORN clinically manifests as pain, exposed necrotic bone, pus discharge, trismus, dryness of mouth, difficulty in talking and eating, orocutaneous fistula and pathological fracture of mandible (Brown *et al*., 1998; Aitasalo *et al*., 1995; McKenzie *et al*., 1993). Over the years, multimodality approach has been used for ORN treatment with variable success rate.

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Early disease is treated by conservative measures like antibiotic therapy, debridement and irrigation whereas surgical resection and reconstruction are reserved for more dreaded presentations not responding to conservative measures (Joshua *et al*., 2013). In present era, HBOT continues to be employed as adjunctive treatment of ORN. HBOT improves oxygenation of tissues leading to repair and healing of necrotic tissue, promotes neovascularisation and helps in control of infection by eradicating microbial growth in affected area (Jedrusik-Pawłowska *et al*., 2010). The purpose of our study was to understand the role of Hyperbaric Oxygen Therapy as an adjunct in improving outcome of treatment of Osteoradionecrosis of Mandible.

MATERIALS AND METHODS

In our institute, prior to starting HBOT, we follow a protocol of examining the patients for presence of any ENT or medical condition like diabetes or hypertension. Any condition, if found, is optimized before subjecting the patient to HBOT. The records of patients with history of head and neck cancers, who received HBOT for mandibular ORN at PGIMER, Dr RML hospital during the period 2015 to 2017 were evaluated. The subjects underwent 30 sessions of 2.5 ATA for 60 min, five times a week in a monoplace hyperbaric chamber.

Patients who did not complete 30 sittings or had incomplete records were excluded from the study. The features noted include patient's age, sex, primary tumour, type and dose of anti-cancer therapy received, time between radiation treatment and onset of ORN, history of smoking/alcohol , pain, presence of fistula/fracture mandible, pus discharge, trismus, dryness of mouth, difficulty in talking and eating. Effect of HBOT was assessed after 30 sessions on basis of relief in signs (closure of fistula/no exposure of bone/no pus discharge) and relief in symptoms of pain/trismus/dryness of mouth/inability to talk. Patients who did not show significant improvement with HBOT underwent sequestrectomy/ resection/ flap cover. Further 10-15 sittings of HBOT were given to them post-operatively and patients were reassessed. At the end of HBOT (either alone or in combination with surgery), overall well-being was assessed by the extent of relief of signs and symptoms. Relief in ≥5 signs and symptoms was rated as Good; ≥3 Fair; ≤2 Poor. All patients were followed up for a period of 12 months for tumour recurrence.

RESULTS

During the study period, 85 patients of mandibular ORN were given HBOT. After reviewing their records, 80 patients fulfilled the inclusion criteria whereas 5 patients were excluded from the study as 2 patients had incomplete records and 3 did not complete 30 sittings of HBOT. Of these 80 patients, 72 were male and 8 were female ranging in age from 35- 75 years (mean age of 53.5 years). The primary site of tumour was tongue (n=27), buccal mucosa (n=20), alveolus (n=12), pharynx (n=11), tonsil (n=9) and larynx (n=1). Table no.1 These patients received radiotherapy either alone or in combination with chemotherapy and/ or surgery. 29 received radiotherapy alone, 22 a combination of radiotherapy and chemotherapy, 23 post-operative radiotherapy and 6 pre and post-operative radiotherapy. Table no.1. The radiation dosage ranged from 50 -70 Gray. These 80 patients had mandibular ORN anywhere from 4 months to 15 years after the completion of radiotherapy. (Mean time of onset of ORN is 3.3years). Patients presented with pain (n= 80), dry mouth (n=53), trismus (n=67), difficulty in talking and eating (n=44), fistula (n=42), exposed bone (n=80) and pus discharge (n=57). Table 2. Patients were assessed after 30 sittings of HBOT. When assessed for relief in symptoms, 91% of patients showed an improvement in pain (VAS score improved by >3), 72% had improvement in dry mouth, 46% in trismus and 54% in difficulty in talking and eating. Table 2

Assessment for relief in signs (condition of wound) after 30 sittings showed closure of fistula in 50%, no exposure of bone 58.75%, cessation of pus discharge in 70.5%. Table no 3. Those who did not show significant improvement underwent sequestrectomy/ resection/ flap cover. 24 (30%) patients improved with HBOT alone. However, 37(46.25%) patients required sequestrectomy and 19(23.75%) underwent surgery for resection/flap cover along with HBOT. Further 10-15 sittings of HBOT were given to them post-operatively Table 4 Overall well-being was assessed by the extent of relief of signs and symptoms after 30 sittings of HBOT. Relief in ≥5 signs and symptoms was rated as Good; ≥3 Fair; ≤2 Poor. In our study 40% patients showed good response, 42.5% fair and 17.5 % poor response Table 5. These patients were followed for up for 12 months for any tumour recurrence.

Effect of HBOT on ORN will be analysed with respect to relief of Symptoms, healing of wound and feeling of well-being

Statistics: Descriptive statistics like Means, Median and proportions were used to describe the study results.

DISCUSSION

ORN is defined as the exposed necrotic bone in an area previously irradiated that fails to heal over a period of 3–6 months1in the absence of tumour recurrence. Radiation exposure causes vascular thrombosis (hypovascularity) leading to hypoxia and cell death of the skin/mucosa and underlying bony element (hypocellularity). This 3-H paradigm, for pathogenesis of ORN, was put forth by Marx and supported the potential therapeutic role of HBOT. Marx incorporated this into a standardized treatment protocol (Wilford Hall HBO ORN protocol) (Marx, 1983). The theory of radiation-induced fibrosis suggests that the key event in the progression of ORN is the activation and dysregulation of fibroblastic activity that leads to atrophic tissue within a previously irradiated area. This alteration is thought to occur earlier than vascular damage8. In addition, a fibro-atrophic theory proposes that it is the reduced ability of fibroblasts to produce collagen that renders tissues weak and fragile.

The median reporting age for ORN is 13Months (range 2-122months) (Curi, 1997). The risk of developing ORN remains for 231 months after irradiation, and second episodes are unusual (Verna Vanderpuye, 2000). In our study mean time of onset of ORN is 3.3years. It has been seen that ORN is clinically important when it involves chest wall, mandible, pelvis, vertebral column, and skull15. However the incidence of ORN is highest at mandible as comparatively it is more cortical and less vascular and often receives more irradiation.16Unique feature about both, the mandible and the maxilla, is that they are exposed directly to the external environment through the gingival attachment of the teeth. In irradiated field, minor insults such as periodontal disease, pulp infections and dental extractions can result in delayed healing and in some cases develop into osteoradionecrosis. In our study, 27 patients gave history of trauma in the form of dental extraction.

There is a definite correlation between the radiation dose and occurrence of ORN. Increasing the external beam radiation dose above 50 Gray has been shown to significantly increase the risk for developing osteoradionecrosis (Reuther *et al*., 2003). In our study the radiation dose ranged from 50 -70 Gray. The incidence of ORN may be higher for concurrent chemotherapy and radiotherapy (CCRT), whereas it may be lower for intensity-modulated radiotherapy (IMRT). 27% patients in our study received combination of radiotherapy and chemotherapy. Other factors that influence occurrence of ORN are age, primary tumor size, radiation to the posterior mandible, infection, malnutrition, poor oral hygiene, and alcohol and tobacco abuse (Jacobson et al., 2010). It clinically presents as pain, swelling, ulceration, exposed necrotic bone, oro-cutaneous fistula, purulent discharge, sequestrum formation, pathological fracture, trismus and paresthesia (Mainous, 1975; Fattore, 1987). Several staging systems for ORN exist in the literature. However, to date, no single system has been universally accepted. Marx proposed the first ORN staging system based solely on response to HBOT (Marx, 1983).

Table 1. Clinical characteristic of the patients with ORN included in the study

Variable	n =	%
Sex		
• Male	72	90
• Female	08	10
Age Group (years)		
≤50	32	40
≥50	48	60
Mean Age	53.5	
Median	54	
Incidence of ORN according to malignancy site		
• Tongue	27	34
• Larynx	20	25
• Pharynx	01	01
• Alveolus	11	14
• Buccal Mucosa	12	15
• Tonsil	09	11
Prior anticancer treatment in patients with ORN		
• Radiotherapy alone	29	36
• Radiotherapy + chemotherapy	22	27
• Post op radiotherapy	23	29
• Pre& post op radiotherapy	06	08

Table 2. Relief in symptoms after HBOT in patients with ORN

Symptoms	n	%
Pain (VAS score improves by >3)	73/80	91
Dry mouth	38/53	72
Trismus	31/67	46
Difficulty in talking and eating	24/44	54

Table 3. Relief in signs (condition of wound) after 30 sittings of HBOT

Variable	n=	%
Closure of fistula	21/42	50
No exposure of bone	47/80	58.75
Cessation of pus discharge	40/57	70.5

Table 4. Treatment outcomes of HBOT for ORN

S. No	Treatment	No. of patients
1	HBOT alone	24 (30%)
2	HBOT and sequestrectomy	37 (46.25%)
3	HBOT and resection / flap cover	19 (23.75%)

Table 5. Patients showing improvement in overall wellbeing after HBOT

Overall well being	n=	%
Good	32	40
Fair	34	42.5
Poor	14	17.5

Relief in ≥5 signs and symptoms is Good; ≥3 Fair; ≤2 Poor.

Instead, we preferred a simple and quickly applicable classification by Notani *et al*. which does not rely on any knowledge of clinical progress or response to treatment. Notani classification is based on Clinical features of ORN (Shaw, 2010).

I -ORN confined to dentoalveolar bone.

II - ORN limited to dentoalveolar bone or mandible above the inferior dental canal, or both.

III- ORN involving the mandible below the inferior dental canal, or pathological fracture, or skin fistula.

We included patients of all three stages in our study. HBOT continues to be employed as adjunctive treatment of all stages of ORN along with surgical interventions like sequestrectomy, resection and reconstruction. This is owing to the fact that HBOT improves oxygenation of tissues enhancing healing of necrotic tissue, controlling infection as HBO is bacteriostatic and bactericidal for many microorganisms6 Additional advantages of HBOT are vasoconstriction, reduction of edema, phagocytosis activation and an anti-inflammatory effect. Long-term effects include stimulation of collagen production by fibroblasts, osteoneogenesis and, most important, neovascularization (Chouinard, 2016; Novaleski, 2008). The induced angiogenesis becomes detectable after 8 sessions. At 20 sessions, it reaches a plateau at 80-85% of non-irradiated

tissue vascularity. The changes induced by HBO therapy on the tissue's oxygen pressure appear to be largely permanent, as, 3 years after completion of HBO treatment, oxygen pressure in the tissue has been observed to be 90% of what it was at the end of the treatment (Novaleski, 2008). Similar multimodal approach was used in our study. 24 (30%) patients improved with HBOT alone. Those who did not show significant improvement underwent sequestrectomy/ resection/ flap cover. 37(46.25%) patients required sequestrectomy and 19 (23.75%) underwent surgery for resection/flap cover along with HBOT. Further 10-15 sittings of HBOT were given to them post-operatively and overall well-being was assessed by the extent of relief of signs and symptoms after 30 sittings of HBOT. Relative contraindications for HBO therapy are claustrophobia, seizure disorder, upper respiratory tract infection, chronic sinusitis and history of spontaneous pneumothorax (Novaleski, 2008). Absolute contraindications are, history of bullous pulmonary disease, congenital pulmonary blebs, untreated pneumothorax and poorly controlled chronic heart failure (Mayer *et al*., 2005). 21 As per our hospital protocol prior examination is done to rule out all the possible contraindications. The principal disadvantages related to HBO therapy are its high cost, the limited treatment locations available, the fact that it is time-consuming (thus difficulty in getting patients' compliance) and that it may delay the definitive treatment (Fattore, 1987).

Conclusion

HBOT alone and as an adjunct to surgery shows encouraging results. Our study corroborates the existing literature on the potential benefit of HBO as an adjunctive treatment of ORN.

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