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Hyperbaric Oxygen Therapy for Head and Neck Irradiated Patients with Special Attention to Oral and Maxillofacial Treatments

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Abstract

Although radiation therapy is a common treatment for head and neck cancer, osteoradionecrosis (ORN) represents a major complication during or after treatment. Hyperbaric oxygen is often mentioned as a prophylactic and therapeutic treatment for ORN. In this article, we review the literature on hyperbaric oxygen therapy in head and neck irradiated patients. The widespread use of such therapy for the prevention and treatment of ORN appears to be based mainly on personal beliefs and experience, as no consensus exists in the scientific literature about its efficacy. Randomized controlled trials are, thus, needed to assess the real impact of hyperbaric oxygen therapy in head and neck irradiated patients. More fundamental research is also needed to clarify the pathophysiology of ORN, which in turn would help identify appropriate treatments.

Radiation therapy is a common treatment modality for head and neck cancer. However, high-dose radiation therapy induces many side effects, such as xerostomia, dysgeusia, dysphagia, mucositis, radiation caries, fibrosis, reduced mouth opening and candidiasis.[1] Surgical interventions in irradiated fields may also result in infections, delayed healing and dehiscence. One of the most severe complications of radiation therapy is osteoradionecrosis (ORN), which can occur during or after treatment. Special measures are required to prevent and treat it, and hyperbaric oxygen therapy is often mentioned in this context. In this article, we present a review of the literature on hyperbaric oxygen therapy in head and neck irradiated patients, with special attention to oral and maxillofacial treatments.

Head and Neck Radiation Therapy

The goal of radiation therapy is to eradicate tumour cells. Cells dies as a result of direct damage to their genetic material, but mainly through the action of free radicals (mainly hydroxyl radicals) generated by the irradiation, which also damage cells' DNA by oxidative reactions.[1] Free radicals interact with lipids and also affect proteins by changing their structure, modifying membrane permeability.[2] Even though rapidly dividing cells are the most affected by radiation, permanent damage is also observed in surrounding normal tissue. Recent advances in radiation therapy have reduced damage to surrounding

healthy tissues, but have not eliminated it completely.[1]

The main problem resulting from radiation therapy seems to be tissue hypoxia, which is caused by the gradual loss of microvasculature.[3] In 1983, Marx presented the 3-H concept, stipulating that progressive fibrosis and obliterative endarteritis lead to a hypovascular, hypocellular and hypoxic environment (hence the name 3-H).[4] In such an environment, "early" and "late" tissue damage may occur: early damage occurring a few weeks to a few months following exposure and late damage, which is more severe and considered irreversible, occurring several months to years following irradiation.[3]

Other known effects of radiation therapy on tissues are decreased bone marrow proliferation, a reduction in the number of periosteal and endothelial cells and the production of an extracellular matrix, mostly composed of collagen.[5] Finally, radiation therapy seems to have a direct impact on osteoblast-like cells, altering their proliferation, differentiation and sensitivity to apoptogens.[6]

Osteoradionecrosis

First reported by Regaud in 1920,[5] ORN is generally defined clinically as the presence of "exposed irradiated bone tissue that fails to heal over a period of 3 months without a residual or recurrent tumor."[7] Marx gives a similar definition, but with a healing period of 6 months.[4,8] The prevalence of ORN ranges from 0.9% to 35% among head and neck irradiated patients and is 3 times more frequent in men than in women.[5]

Clinical features of ORN are exposed necrotic bone, sequestra, ulceration, pain, purulent discharge, swelling, trismus, paresthesia, orocutaneous fistulae and pathologic fracture.[8,9] ORN is more frequently observed in the lower jaw than the upper, as the former is more cortical and less vascular and often receives more irradiation than the latter.[10] ORN mainly occurs 4 months to 2 years after completion of radiation therapy.[7]

Factors affecting the development of ORN are primary site of tumour; tumour stage; type of surgery; field, type and dose of radiation; time since irradiation; chemotherapy; premorbid state of dentition; chronic prosthesis trauma; surgical procedure to the jaw; nutritional status; and alcohol and tobacco use.[5,9-11]

According to Marx's theory, bone affected by radiation therapy represents a hypovascular, hypocellular, hypoxic tissue. Once exposed to the oral cavity following a tooth extraction or any other trauma, that bone has poor healing potential and is more prone to necrosis. An imbalance between the normal homeostasis of cell repair and cell death, collagen synthesis and collagen breakdown could be responsible for this phenomenon.[8]

A second theory postulates that the suppression of osteoclasts by radiation directly affects bone turnover.[11] This alteration is thought to occur earlier than vascular damage.

In addition, a fibro-atrophic theory proposes that it is the reduced ability of fibroblasts to produce collagen that renders tissues weak and fragile.[1,7,11,12]

Treatment

The main goals of ORN treatment are to restore vascularization, allow the wound healing process to occur and, thereafter, maintain normal tissue homeostasis. Criteria for success are a stable asymptomatic condition, normal function, normal bony contour, maintenance of overlying oral mucosa and good esthetics.[8]

The choice of treatment is determined by the severity of the ORN. Conservative treatment consists of debridement (the removal of all necrotic tissue being important to allow self-healing), irrigation and prophylactic antibiotic therapy to prevent secondary infection. Such a conservative approach is reserved for emerging or localized lesions.[9] Patients with pathologic fracture, an orocutaneous fistula or full thickness devitalized bone do not respond to this treatment.[8,13] Surgical approaches, such as resection, reconstruction with bone graft and fistulectomy, are indicated for these more severe cases.

Hyperbaric Oxygen Therapy

More commonly used for the treatment of air embolism, carbon monoxide poisoning and compartment syndrome, hyperbaric oxygen (HBO) therapy is also used as an adjuvant to both conservative and surgical treatment of ORN. It consists of inhaling 100% oxygen at an elevated pressure (above 1.5 atmospheres). 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[4] and if HBO therapy is used as a preventive method, the protocol is daily sessions for 20 days before surgery and 10 after.[11,14]

HBO treatments bring oxygen to the hypoxic tissue by increasing the blood–tissue oxygen gradient; this favours the wound healing process by facilitating the reconstruction of irradiated tissues and preventing necrosis.[8] In addition, HBO is bacteriostatic and bactericidal for many microorganisms.[13]

Short-term effects of HBO therapy include vasoconstriction, reduction of edema, phagocytosis activation and an anti-inflammatory effect. Long-term effects include stimula-

tion of collagen production by fibroblasts, osteoneogenesis and, most important, neovascularization.[3,13] 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.[3]

Relative contraindications for HBO therapy are claustrophobia, seizure disorder, upper respiratory tract infection, chronic sinusitis and history of spontaneous pneumothorax.[3] Absolute contraindications are optic neuritis, history of bullous pulmonary disease, congenital pulmonary blebs, untreated pneumothorax and poorly controlled chronic heart failure.[3,11,15] The presence of an active tumour was once a contraindication,[15] but Feldmeier and colleagues,[16] after reviewing the available clinical data, concluded that there is no evidence that HBO therapy induces tumour cell growth.

Known HBO therapy complications, with a global prevalence of 7.8%, are transient myopia, middle-ear barotrauma, pneumothorax, arterial air embolism, oxygen toxicity seizure, exacerbation of acute viral infection, pulmonary oxygen toxicity and acute pulmonary edema.[1,11,15]

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.[8]

Considerations for Oral and Maxillofacial Treatments

Tooth Extractions

Because dental surgery appears to be 1 of the most important factors contributing to ORN, follow-ups are an important prevention measure. All infected or non-salvageable teeth should be removed before radiation therapy. Extraction should be carried out at least 21 days before the beginning of radiation therapy to allow the initial healing process to occur and to enable newly formed tissues to better withstand irradiation. Otherwise, but less optimally, teeth should be extracted within 4 months of therapy completion after which ORN risks increase. Outside these periods, alternatives, such as restoration or root canal treatment, are preferred. According to Marx, HBO therapy should be used when teeth need to be extracted outside these periods.[11]

A recent systematic review[15] concluded that HBO therapy is indicated after extraction of mandibular teeth located in the irradiated field among patients who received a radiation dose greater than 60 Gy. However, despite HBO therapy, irradiated patients may still develop ORN. In a study involving 40 irradiated patients receiving a prophylactic HBO treatment, 6 of 371 extraction sites (1.6%) did not heal after 1 year.[17] In another study of 20 patients receiving pre- and post-operative HBO treatment, the reported ORN prevalence was 15.8%, 6 months after extraction.[18]

Unfortunately, most investigations are cohort studies rather than randomized controlled trials, which makes it difficult to evaluate the real impact of HBO therapy on ORN. In the only randomized trial reported so far, HBO treatment was found to be superior to prophylactic antibiotic therapy. Among patients treated with penicillin before and after extraction or with prophylactic HBO treatment without antibiotics, a significant difference in favour of the HBO treatment was noted: 5.4% versus 29.9% ORN 6 months after surgery.[14] This study supports the efficacy of HBO therapy in reducing ORN.

Based on all the available evidence, a recent Cochrane review concluded that HBO treatment helps prevent ORN after dental extraction.[19]

Dental Implants

Dental implants improve the quality of life of irradiated patients, particularly those who are edentulous or have ill-fitting dentures. Fortunately, radiation therapy is no longer an absolute contraindication for dental implant surgery.[20,21]

In a 16-year study of 78 patients requiring dental implants, Granström and colleagues[22] observed implant failure rates of 13.5% in non-irradiated patients, 53.7% in irradiated patients and 8.1% in irradiated patient receiving HBO therapy, suggesting a positive effect of HBO treatment on dental implant survival rate.

On the other hand, in a randomized trial comparing prophylactic antibiotic therapy with and without HBO therapy among 26 patients requiring dental implants, Schoen and colleagues[21] observed no statistical difference between the 2 protocols with respect to implant survival rate, peri-implant bone loss and ORN development.

Thus, there is no consensus on whether HBO therapy should be carried out before placement of dental implants in head and neck irradiated patients.[23-25]

Improvement in Quality of Life of Irradiated Patients

Using various questionnaires to measure quality of life of irradiated patients receiving HBO therapy as an ORN treatment or as a prophylactic measure, Harding and colleagues[26] observed a significant reduction in pain and xerostomia and an improvement in chewing ability and

global health. They concluded that HBO therapy improves quality of life for these patients. However, no control group was included in their study.

Schoen and colleagues[21] also analyzed the impact of HBO therapy on the quality of life of patients by comparing those treated with prophylactic antibiotics with or without HBO. The assessment, using various questionnaires, revealed that the group treated solely with prophylactic antibiotics had a better overall quality of life. The fact that HBO therapy is time-consuming and that complications related to the treatment can occur may alter the general quality of life of patients.

Efficacy of HBO Therapy

Although HBO therapy is used for the prevention and treatment of ORN based on Marx's theory, recent theories about the origin of ORN raise doubts about the appropriateness of HBO therapy. A randomized placebo-controlled double-blind study was conducted to evaluate the effect of HBO therapy on ORN.[27] The treatment group received 30 sessions of HBO before and 10 after surgery when such a treatment was needed. The controlled group was treated in the same manner but with a gas similar in composition to normal room air. The study was stopped after enrolling 68 patients when an interim analysis revealed a lower recovery rate in the HBO group (19.3%) compared with the placebo group (32.4%).

These results cast doubts on Marx's theory explaining ORN in terms of hypovascularity, hypocellularity and hypoxia. The fact that HBO therapy seems to inhibit osteoblast growth, by increasing apoptosis and potentiating cell-cycle arrest, represents an important element to take into consideration when trying to find an alternative explanation.[6]

Controversy in the Literature

Today, the widespread use of HBO therapy for ORN treatment appears to be based on personal beliefs and experience rather than convincing scientific evidence. No consensus on its efficacy exists in the literature, which consists mainly of poorly controlled trials and cohort studies.[28] The only available randomized controlled study (without a placebo group), conducted by Marx, demonstrates the benefit of HBO therapy over antibiotic therapy in the prevention of ORN following dental extraction.[14] These results contrast with those of Annane and colleagues,[27] which showed a negative effect of HBO therapy in the treatment of ORN. However, the patients enrolled in this study received HBO or placebo twice a day, which differs from the usual 1 session a day protocol. Overall, both studies dealt with relatively small cohorts (about 30 patients) and neither took into consideration the previous dental condition of the patient or the severity of the ORN, resulting in a low level of evidence. With these conflicting studies, it is, thus, not possible to draw conclusions on the efficacy of HBO therapy in the prevention and treatment of ORN.

In recent years, various substances have been tested as alternative treatments for ORN, namely pentoxifylline (a peripheral vasodilator), vitamin E and clodronate (a bisphosphonate).[7,8,13] These treatments are based on different pathophysiological theories of ORN: osteoclast suppression or fibro-atrophic process. The fact that these approaches are producing positive results raises doubts about the veracity of the theory behind HBO treatment and, thus, the efficacy of HBO treatment itself.

Conclusion

This review of the literature shows that more randomized controlled trials are needed to assess the true impact of HBO treatment for head and neck irradiated patients. No clear positions exist on the use of HBO as a preventive or curative treatment for ORN. More basic research is needed to clarify the pathophysiology of ORN, which would help identify appropriate treatment guidelines.

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