HYPERBARIC OXYGEN THERAPY AS ADJUNCTIVE STRATEGY IN RADIOTHERAPY

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Abstract
In the previous several decades the radiotherapy has been widely used in the treatment of the broad spectrum of the malignant and non-malignant diseases. Similarly to other therapies, however, radiotherapy has its limits too. These include, in particular, the hypoxic environment of tumor tissues, which reduces its effectiveness. Another problem consists of secondary radio-necrosis. Both of these limits of radiotherapy can be to some extent eliminated with the help of hyperbaric oxygen therapy. Previous case studies have demonstrated a significant therapeutic effect of hyperbaric oxygen therapy in the treatment of these complications. Still, there are no standard treatment procedures or consensus guidelines. It is necessary to carry out clinical studies with a larger number of samples and more detailed selection criteria.

Keywords: Hyperbaric oxygen therapy. Radiotherapy. Hypoxia. Radionecrosis. Radiosensitivity.

1 Introduction

In the case of the cancer diseases, the hyperbaric oxygen therapy (HBOT) is auxiliary and not primarily life-saving treatment. HBOT is the therapeutic method in which the patient inhales 100% oxygen at a pressure of more than 1 atmosphere (1 ATA; 101.325 kPa) in a specially treated hyperbaric chamber. During HBOT, oxygen dissolves in all body fluids (e.g. blood plasma, lymph, cerebrospinal fluid) and, moreover, penetrates into ischemic areas deeper than at normobaric pressure. Increased oxygen concentrations in the body, together with higher pressures, are complex, giving HBOT unique therapeutic options. HBOT stimulates aerobic metabolism, reduces lactate production, eliminates local acidosis, allows for greater diffusion of oxygen into tissues, bactericidal effects on anaerobic bacteria, regenerates nerve cells, reduces edema, and many others [1-6]. Thanks to its multiple and general effect on the all tissue and organ systems it seems however to be an important tool of adjuvant therapy in the treatment of adverse side effects of radiotherapy [1, 3, 7].

Radiation therapy has proven to be effective in the treatment of malignancies. The goal of the therapy is to irradiate tumors with minimal adverse effects on the surrounding normal tissue. This is difficult to achieve and in practice, there is usually some degree of residual damage to the tissues after radiotherapy. Theoretically, it is possible to destroy all malignancies if the dosage of radiation is raised to high levels. With the limitations of the human body's tissue tolerance to radiation, optimal dosage schedules are followed that provide an acceptable benefit/damage ratio for the patient. Radiation-induced tissue necrosis is a complication even when accepted dosage schedules are followed [1].

As we mentioned in previous work [6], in clinical practice, the use of HBOT in oncology focuses primarily on the treatment of late effects of radiotherapy (radiation necrosis), either bone (osteoradionectosis) or soft tissues or so-called radiosensitization. In the past, HBOT has also been shown to reduce unpleasant symptoms after irradiation.

2 Radiotherapy

Radiotherapy uses ionizing radiation to treat the tumor with minimal adverse side effects on the surrounding healthy tissue. X-rays and gamma rays are able to penetrate the depth of tissue and destroy tumor cells from deep layers as well. Radiotrherapy induces direct lesions in DNA or biological molecules that eventually affect DNA. Thus, in tissue irradiation, cellular changes occur mainly at the level of genetic information, leading to a change in metabolic processes and cell metabolism. These changes result in damage to the cell until its disappearance. However, irradiation does not only reduce the number of tumor cells but also partially damages healthy cells present in the irradiated area, which may be responsible for very serious acute or late posttraumatic diseases [8].

Acute side effects are already present during radiotherapy and last up to three months after it is terminated. The most widespread adverse reactions occur in rapidly proliferating tissues such as skin epithelium, mucous membrane and hematopoietic system. Individual acute reactions are directly related to the amount of radiation exposed and the duration of therapy. Late side effects occur primarily in low-turnover tissues, i.e., connective tissue, vessels, lungs, hearts, kidneys, nerve tissue, liver and muscles. They may occur suddenly or sequentially, in some cases as the result of a more pronounced acute reaction predicting the transition to the late reaction [9].

The tissues react to ionizing radiation in different ways.The type and degree of complications depend on the irradiated area, the extent of the irradiated area and the radiation dose. They may appear locally, for example, in the form of inflammatory changes in the skin, or generally as malaise, weakness, lack of appetite, and the like. The incidence of these complications is dependent on many factors, among which the most significant predisposing factors are the radiation dose, infection or surgery in the irradiated area, prior ischemia (local hypoxia), immunodeficiency, alcoholism, smoking, diabetes, hypertension, steroid therapy, nutritional status and the age of the patient [8, 9].

3 The rationale for use of HBOT for radiotherapy

The presence of hypoxic tumor cells is widely regarded as one of the main reasons behind the failure to control malignant tumors with radiotherapy treatments. Since hyperbaric oxygenation improves the oxygen supply to the hypoxic tumor cells, HBOT has previously been used in combination with simultaneous radiotherapy to treat malignant tumors. In some clinical trials, significant improvements in local control and survival have been seen in cancers of the head and neck and the uterine cervix. However, the delivery of simultaneous HBOT and radiotherapy is both complex and time-consuming, with some trials reporting increased side effects. As a result, the regimen of HBOT in combination with simultaneous radiotherapy has yet to be used as a standard treatment for malignant tumors. In recent years, however, radiotherapy immediately after HBOT has been emerging as an attractive approach for overcoming hypoxia in cancer treatment. Several studies have reported that radiotherapy immediately after HBOT was safe and seemed to be effective in patients with high-grade gliomas. Also, this approach may protect normal tissues from radiation injury. To accurately estimate whether the delivery of radiotherapy immediately after HBOT can be beneficial in patients with high-grade gliomas and other cancers, further prospective studies are warranted [7].

There is no satisfactory treatment of radiation necrosis using the available conventional methods. It is difficult to provide adequate nutrients and oxygen to the devascularized tissuess. Radiation ulcers are painful and use of narcotic analgetics can lead to to addiction. Reconstructive sugery in the radiated areas has a high failure rate due to healing problems. Frustration with the use of conventional methods has led to the trial use of HBOT in the management of radiation necrosis. HBOT raises the tissue pO_2 to within the normal range and stimulates collagen formation at wound edges. This, in turn, enhances the formation of new microvasculature. This provides reepitalization of small ulcers and provides a better nutritive bed to support grafts and pedicle flaps. Tissue oxygen studies have shown that angiogenesis becomes measurable after 8 treatments with HBOT, reaches a plateau at 80-85% of non-radiated tissue vascularization after 20 treatments, and remains at this level whether or not HBOT is continued [1].

Radiation exposure may, more frequently in the long term, cause severe injuries to the afflicted tissues, due to a phenomenon usually termed as fibroatrophic effect. According to this dictum, beside vascular alterations, severe fibrosis and cellular depletion account for the morbidity and mortality observed following irradiation. HBOT enhances neovascularisation both through angiogenesis and vasculogenesis and also relieves fibrosis by improving the oxidative stress imbalance through enhanced production of antioxidants. Uzun et al. [10] presented a case report of 59-year-old male patient presented with a large deep non-healing wound over his left scapula, which had occurred following a longcourse of radiotherapy and did not heal with standard measures for 2 months. Besides standard wound care management the patient received 40 sessions of HBOT, at 2.4 ATA, 2 hours each, in a multiplace chamber. The wound showed a gradual progress towards healing over the course of HBOT and achieved a good granulating base at the end of 3 months, whereafter it was closed by primary intention. On examination, the length, width and depth of the wound were 20 cm, 10 cm and 2.5 cm, respectively. The wound base was granulated and not infected as evidenced by wound culturing. In other study, Fernández Canedo et al. [11] reported three cases of radiation-induced skin ulcers in which HBOT was administered in 90-min sessions, 5 days a week at 2.4 ATA in a multiplace hyperbaric chamber. Authors conclusions stated that HBOT is an outpatient treatment that does not displace other classical treatments but may be used as an adjunct therapy.

HBOT is considered a treatment option in patients with chronic radiation-induced proctitis after pelvic radiation therapy. Refractory cases of chronic radiation-induced proctitis include ulceration, stenosis, and intestinal fistulas with perforation. Appropriate treatment needs to be given. Yoshimizu et al. [12] assessed in their study the efficacy of HBOT in five patients with radiation-induced rectal ulcers. Significant improvement and complete ulcer resolution were observed in all treated patients; no side-effects were reported. HBOT has a low toxicity profile and appears to be highly effective in patients with radiation-induced rectal ulcers. However, HBOT alone failed to improve telangiectasia and easy bleeding in four of the five patients; these patients were further treated with argon plasma coagulation (APC). Although HBOT may be effective in healing patients with ulcers, it seems inadequate in cases with easy bleeding. Altogether, these data suggest that combination therapy with HBOT and APC may be an effective and safe treatment strategy in patients with radiation-induced rectal ulcers.

Laryngeal radionecrosis is one of the most troublesome late complications of radiotherapy, because it is frequently resistant to treatment and laryngectomy is required in the worst case. Abe et al. [13] report a case of laryngeal radionecrosis, successfully treated by use of HBOT, in which laryngectomy was avoided. A 67-year-old

male received radical chemoradiotherapy (CRT) for mesopharyngeal cancer, which included radiotherapy with a total dose of 71.4 Gy/38 Fr and chemotherapy with CDDP + S-1. He developed dyspnea and throat pain 9 months after completion of CRT. Laryngoscopy revealed vocal cord impairment because of severe laryngeal edema. He was diagnosed as having laryngeal radionecrosis and initially received conservative therapy combined with antibiotics, steroids, and prostaglandins. Because his dyspnea was persistent despite this treatment, HBOT was administered 20 times, and resulted in complete remission of the dyspnea.

Although hyperbaric oxygen is used to treat chronic radiation tissue injury, clinical evidence supporting its efficacy has been limited to date. Hampson et al. [14] reported prospectively collected patient outcomes from a single center's large experience using hyperbaric oxygen to treat chronic radiation injury. From 2002 to 2010, a total of 525 patients received treatment for 1 of 6 forms of radionecrosis analyzed. After excluding 114 patients for incomplete records or treatment courses or for previous receipt of HBOT, records of 411 patients were retrospectively reviewed in 2010, and outcomes were regraded by a second board-certified physician. A positive clinical response was defined as an outcome graded as either "resolved" (90%-100% improved) or "significantly improved" (50%-89% improved). The outcomes of 411 patients collected prospectively over 8 years strongly supported the efficacy of HBOT for the 6 conditions evaluated. A positive outcome from hyperbaric treatment occurred in 94% of patients with osteoradionecrosis of the jaw (n = 43), 76% of patients with cutaneous radionecrosis that caused open wounds (n = 58), 82% of patients with laryngeal radionecrosis (n = 27), 89% of patients with radiation cystitis (n = 44), 63% of patients with gastrointestinal radionecrosis (n = 73), and 100% of patients who were treated in conjunction with oral surgery in a previously irradiated jaw (n = 166).

Despite recent advances in radiotherapy, osteoradionecrosis remains a common and difficult complication of radiation therapy cancer patients. Available treatment options are complementary to its complex pathophysiology and the currently available theories of osteoradionecrosis development. The efficacy of HBOT has recently been questioned, and therapies targeting the fibroatrophic process have become a focus of osteoradionecrosis treatment. The recently proposed fibroatrophic theory has challenged the traditional hypovascular-hypoxic-hypocellular theory as the mechanism of osteoradionecrosis. No gold standard treatment or consensus guidelines exist; though a combination of therapeutic strategies should be considered, taking into account the severity of disease and individual patient characteristics. Medical management targeting this fibroatrophic process offers promising results, but has yet to be confirmed with robust clinical trials. The routine use of HBOT is not substantiated in the literature, but may be justified for select patients. Systemic steroids may also have a role, though data are limited [15]. Published data on osteoradionecrosis of the jaw are difficult to compare because of the lack of a universally accepted classification and staging system, and the literature on the use of HBOT to either prevent or successfully manage osteoradionecrosis of the jaw is controversial and inconclusive [16].

4 Conclusion

Previous results show appropriate applicability of the hyperbaric oxygen therapy in the treatment of late effects of radiotherapy (radiation necrosis), either bone (osteoradionectosis) or soft tissues or so-called radiosensitization. Significant reserves, however, remain in the field of the knowledge of the detailed molecular mechanisms of influence of hyperbaric oxygen therapy used as adjuvant therapy together with the radiotherapy. Previous case studies have yielded promising results. However, it is necessary to carry out further studies with a larger number of individuals that would also reveal the relationships between the individual metabolic-physiological parameters during and after therapy. A more significant problem is the number of individuals required for statistical data processing. There are only very few hyperbaric oxygen therapy units that have the ability to conduct clinical trials in a non-commercial scale. Most hyperbaric oxygen therapy workplaces are commercially focused and do not carry out clinical research. Therefore, they are unable to develop new standard therapeutical procedures and guidelines. This leads to stagnation and application of established procedures.

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