American Research Journal of Oncology
Volume 3, Issue 1, 1- 6 Pages
Research Article | Open Access

AMERICAN RESEARCH JOURNALS
An Academic Publishing House

Research Advances in Hyperbaric oxygen Therapy use in cancer: A Review

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ABSTRACT

Cancer is still an important health problem worldwide with limited effective treatment, being the second cause of death in the USA. Hyperbaric oxygen therapy (HBOT) has long been investigated as an adjuvant treatment that could potentiate the effects of radio- and chemotherapy during the treatment of various types of cancer. In this review, we examine the most recent studies conducted in certain types of cancers, from the year 2012 till 2020. These suggest HBOT can be used as an adjuvant cancer treatment in combination with other therapies, can positively influence the immune system,and can also be used as a therapy for wound care and management.

KEYWORDS: Hyperbaric oxygen therapy, cancer treatment.

ABBREVIATIONS: Hyperbaric oxygen therapy (HBOT), World Health Organization (WHO), glioblastoma multiforme (GBM), Reactive Oxygen Species (ROS), Hypoxia-inducible factor 1-alpha (HIF-1□), tumor necrosis factor-alpha (TNF-□), interleukin-1 beta (IL-1□), vascular endothelial growth factor (VEGF), matrix metallopeptidase-9 (MMP-9) and nuclear factor-kappa B (NF-□B), temozolomide (TMZ)-loaded porous silicon nanoparticles (TMZ/PSi NPs).

BACKGROUND

Cancer is defined by the World Health Organization (WHO) as the uncontrolled growth and spread of cells found within any part of the human body, which often can invade the surrounding tissues and metastasize (WHO, 2018). Uptodate, cancer is still an important health problem worldwide, being the second cause of death in the USA (Siegel et al. 2018). The hyperbaric oxygen therapy (HBOT) consists of intermittent administration of 100 % oxygen to an individual, with the purpose to increase the amount of oxygen dissolved in blood at pressures greater than 1 atm (Daruwalla et al., 2006; Yan et al., 2015; Stępień et al., 2016). This process permits that more oxygen reaches the tissues and oxygenate hypoxic tumor regions (Poff et al., 2015). Currently, HBOT is used to treat several conditions like air or gas embolism, carbon monoxide poisoning, decompression illness, burns, necrotizing soft tissue infections among others (Fife et al., 2016).

HBOT used as an adjuvant modality can improve wound healing, and promote the proliferation of fibroblasts, epithelial cells, and blood vessels in the angiogenesis process (Moen & Stuhr, 2012). Some of the benefits of using HBOT are given because of the law of Boyle and Henry. The first one is related to the volumetric effect of gases, where it is stated that at a constant temperature, the volume of a gas is inversely proportional to the pressure. This principle is very useful for gas embolism treatment. The second is related to the solubility effect of gases, which states that an increase in the partial pressure of a gas such as oxygen, the solubility of the gas increases as well. By augmenting the oxygen supply available, angiogenesis is encouraged, and so is the correction of general and local tissue hypoxia, phagocytosis of neutrophils, bactericidal and bacteriostatic action, and elimination of carboxyhemoglobin (Desola et al., 1998; Fernández et al., 2017; Iriarte et al., 2006).

Some of the adverse effects that might arise from the use of HBOT are related to the toxic effect of oxygen and the higher pressures of its exposure (Fernández et al., 2017). Though very uncommon, HBOT can cause barotraumatic lesions, seizures, and acute pulmonary edema (Mathieu et al., 2017). The WHO recognizes surgery, radiotherapy or chemotherapy as possible treatments for cancer, but the HBOT is not included within the official information webpage of treatments available for cancer. Nonetheless, HBOT has long been investigated as an adjuvant treatment that could potentiate the effects of radio- and chemotherapy during the treatment of various types of cancer (Al-Waili et al., 2005; Huang et al., 2018; Moen & Stuhr, 2012). HBOT can increase the cytostatic effect of certain drugs, and therefore could render the chemotherapy more effective (Stępień et al., 2016). In this review, we examine the most recent studies conducted in some types of cancers, 2012 till 2020. We will like to propose a new possible mechanistic anticancer approach for HBOT.

CANCER TYPE AND HBOT ROLE

Breast Cancer

Nowadays breast cancer still a major cause of death in women worldwide (Liu et al 2015). A review published in 2012, concluded that the effect of HBOT in breast cancer needed to be further explored because there was only one clinical study available (Moen & Stuhr, 2012). Sletta et al. published a study in 2017, examining the effect of HBOT on tumor growth in breast tumors, evaluating the impact of HBOT on fluorouracil (5FU) efficacy, and the progression to metastasis. The results of the study showed that HBOT considerably decreased tumor growth in triple positive and triple-negative tumors, but there were no differences in 5FU efficacy in comparison with the control group.

Gastric Cancer

Recently, two papers were published exploring the use of Hyperbaric oxygen treatment (HBOT) in SGC7901 cells. In 2017, Qi et al. conducted a study evaluating the effect of HBOT alone on cell proliferation autophagy and oxidative stress, and the results showed that after exposing SGC7901 cells to HBOT, there was an increment in cell proliferation compared with the control group. They concluded that HBOT use alone could boost the proliferation and survival of these cells, and could also inhibit apoptosis via regulating cell autophagy and oxidative stress (Qi et al., 2017). On the other hand, in 2018, Wei et al. published a study exploring the effects of HBOT in combination with melatonin, using gastric cancer cell line SCG7901. The results of the study exhibited more apoptotic cells on the group treated by the combination of HBOT and melatonin, in comparison with the cells treated with melatonin alone. They concluded that HBOT used in combination with melatonin could be a hopeful treatment in gastric cancer (Wei et al., 2018).

Brain Cancer (glioma)

Gliomas are the most prevalent type of intracranial tumor with glioblastoma multiforme (GBM) the most commonly diagnosed intracranial malignant tumor in adults (Huang et al., 2018; Wang et al., 2015). Wang et al. (2015) conducted a study with transplanted gliomas in mice. They found that hyperbaric oxygen treatment alone promoted the growth and also inhibited apoptosis of glioma cells. Further studies conducted in 2018 concluded the same and showed that the pro-oncogenic effect of HBOT on glioblastoma multiforme tumors was related to the reduction of Reactive Oxygen Species (ROS) levels in brain and glioma cells, the generation of T cell immunosuppression, and the promotion of Treg cell production in the thymus (Wang et al., 2018).

On the other side, Qin et al. (2015) reported a study evaluating the effect of HBOT on the growth of glioma in rats, and the authors concluded that HBO alone could promote tumor growth. Another study of gliomas in transgenic mice was published in 2016 by Lu et al., and the authors concluded that HBOT could inhibit glioma cell proliferation, inflammatory cell infiltration, and could even function as an adjuvant with Nimustine therapy. This was accomplished by an increase in tumor tissue oxygenation, and suppression of the Hypoxia-inducible factor 1-alpha (HIF-1α), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), vascular endothelial growth factor (VEGF), matrix metallopeptidase-9 (MMP-9) and nuclear factor-kappa B (NF-κB).

Further studies also suggest that the addition of HBOT to radio- and chemotherapy may be beneficial to patients with GBM. 2-year overall survival of 46.5% and progression-free survival rates of 35.4% was reported in a study conducted in 2017 and concluded that radiotherapy immediately after HBOT (60 - 90 minutes at 2 ATA) could increase the sensitivity of hypoxic tumor cells to radiotherapy (Huang et al., 2018; Yahara et al., 2017). Most recent studies conducted by Xie et al. (2018) suggest that the combinational treatment of temozolomide (TMZ)-loaded porous silicon nanoparticles (TMZ/PSi NPs) and HBOT could become a promising therapeutic strategy for glioma tumors in rats. The results concluded that the concentration of oxygen in the tumor was improved, and the antitumor rate was increased to 84.2% in the TMZ/PSi NPs combined with the HBOT group. The viability of induced hypoxic glioma cells decreased, and the cell cycle was arrested at the G2/M phase in response to TMZ/PSi NPs treatment with HBO, causing an antitumor effect (Xie et al., 2018). These conflicting results may arise from the angiogenesis effect of HBOT. Increased angiogenesis can enhance tumor growth if patients maintain a high carbohydrate intake instead of a low carbohydrate ketogenic diet, that will favor an augmented non oxidative glycolysis. This type of nonoxidative energy generating system is the main source of ATP of the cancer cells (Gonzalez et al., 2012)

Head and Neck cancer

Paniello et al. (2014) examined the effect of hyperbaric oxygen therapy in head and neck cancer. They conducted a study using mouse model squamous cell carcinoma, and the results showed that the two groups treated with HBOT presented higher tumor volumes and faster growth rates in comparison with the control groups. It was then reasoned and theorized that HBOT accelerates the growth of squamous cell carcinoma (Paniello et al., 2014). Moreover, in a research study published in 2017, Sønstevold et al. reported to have seen no change in blood density or morphology of the skin, muscle, salivary gland, gingiva or periodontal membrane tissues between control and HBOT rats, after radiation. This reinforced the suggestion that HBOT does not affect radiation injury of the mandibular area in rats, specifically within 12 weeks after irradiation (Sønstevold et al., 2017). Sultan et al. (2017) recommended in another study that, since there is no conclusive evidence to support the use of HBOT for prevention or management of osteoradionecrosis of the jaw (ORN), a common and serious complication of radiation therapy, then it should not be routinely used.

A study protocol for a randomized controlled trial is being conducted this year to evaluate if ORN of the irradiated mandible can be prevented with hyperbaric oxygen (HOPON) (Shaw et al., 2018). On the other hand, in a more recent study, Arıcıgil et al. (2017) used biochemical and histopathological methods in albino rats to investigate the efficacy of HBOT against the inflammatory effects of radiotherapy in blood and laryngeal tissues, when radiotherapy and HBOT were administered on the same day. Results showed that serum tumor necrosis factor-alpha, interleukin-1beta, and tissue inflammation levels were significantly higher in the radiotherapy-alone group, whereas interleukin-10 was higher in the radiotherapy-HBO group (Arıcıgil et al., 2017). They concluded that inflammatory cytokines and tissue inflammation can be reduced in an early period of radiation injury when given HBOT and radiotherapy the same day.

HBOT and radiation therapy can be used to increase the efficiency of treating patients with single brain metastasis (Tao J et al. 2019). HBOT decreases the harmful effects of radiation therapy and thus increases the quality of life of Head and neck cancer patients. (Teguh et al., 2009). Osteoradionecrosis of the mandible occurs in patients with head and neck cancer undergoing radiation therapy. HBOT is useful in the improvement of osteoradionecrosis in such patients. (Gupta P et al., 2013).

Skin cancer

A study published in 2014 evaluating the effect of HBO on tumor cells. The results demonstrated an increase in tumor volume in the group treated with HBO in comparison with the control group. They mention that HBO accelerated tumor proliferation and advanced tumor progression in skin carcinogenesis (Doguchi et al., 2014). Several studies of HBOT for radiation-induced skin ulcers have been conducted.

The largest of such studies included 58 patients, and reported a great response, with a resolution in 25% of the patients and an improvement of 50–90% in half of the patients (Hampson et al., 2012). In more recent cases reported, HBO was utilized as a wound-healing therapy in such ulcers caused as a result of radiation in patients who were diagnosed with non-melanoma skin cancer (Fernández et al., 2017). The therapy implemented consisted of 90-min sessions, 5 days a week at 2.4 absolute atmospheres in a multiplace hyperbaric chamber. As a complementary treatment, HBOT showed a beneficial outcome in wound healing (Fernández et al., 2017).

Radical vulvectomy, a surgical procedure for vulvar cancer, has a high risk of wound dehiscence (Howell et al., 2018). Because patients who undergo such procedures usually receive chemotherapy as a neoadjuvant treatment before the surgery, they can experience improper wound healing as a complicating secondary effect. It has been shown that HBOT before surgery and after radiation (which is given after surgery) can decrease the risk of poor wound healing and tissue necrosis (Howell et al., 2018; Griffiths et al., 2018). A protocol that can be utilized relays in daily sessions of 100% oxygen at 2.0 to 2.5 atm absolute for 90 minutes. In all five reported cases by Griffiths et al. (2018), patients were treated for an average of 58 HBOT sessions (range 44–100), and the mean reduction in wound area after completion of HBO therapy was found to be 76%, (42–95%) with a mean follow up of five months.

Leukemia

There is limited research conducted with regard to the relationship of leukemia with HBOT. In 2014, te Winkel et al. published a review article in which HBOT was used as one of the five adjuvant treatments of osteonecrosis in children and adolescents with acute lymphoblastic leukemia, but its results were inconclusive as to the real effect of each treatment used individually. A recent case report of a patient with leukemia and an invasive rhinocerebral mucormycosis was treated with a multimodal approach that included HBOT, and after three months the metastasis was under control (Dworsky et al., 2018). But again, further research is needed to assess the relationship of HBOT with leukemia.

Some other uses of Hyperbaric Oxygen therapy:

A study was done by Brewer AL et al., 2020 on the effect of HBOT in the treatment of chemotherapy-induced neuropathy in male and female rats. It was found that HBOT could effectively decrease chemotherapy-induced neuropathy in paclitaxel treated rats with no major side effects.HBOT can be used after undergoing hepatectomy to reduce the need for blood transfusions for meeting oxygen requirements. This further reduces ischemic changes and postoperative complications. This also affects the immune system and enhances survival after hepatic surgery in patients with hepatocellular carcinoma (Ueno S et al., 2011). Gastritis induced bleeding can occur following chemotherapy and radiation therapy for esophageal cancer metastasis. HBOT is found to be useful in controlling bleeding in such patients (Asaumi Y et al., 2015). HBOT is effective and useful for the treatment of persistent wounds and radiation-induced tissue injury in patients following sarcoma treatment. (Generaal JD et al., 2020). In a study by Lin LJ et al., 2020 HBOT was effectively used as an adjuvant therapy to treat stage 0 medication induced osteonecrosis of the jaw. (Lin LJ et al., 2020). HBOT, when combined with 5-Aminolevvulinic acid photodynamic therapy, can inhibit human squamous cell carcinoma by inducing A431 cells apoptosis (Mei LH et al., 2018)

CONCLUSIONS

Hypoxia is a critical hallmark of solid tumors and is involved in drug resistance. HBOT is used as an adjuvant treatment for some cancers, as discussed in this review. In summary, the effect of HBOT in breast cancer needs to be further explored because there are few clinical studies available; HBOT used in combination with melatonin seems as hopeful treatment in gastric cancer (Wei et al., 2018); HBOT promoted GBM tumor growth and influenced the immune system by immunosuppressing T cell maturation in the thymus (Wang et al., 2018) although this might be related to the particular oxygen pressure applied, and the combinational treatment of TMZ/PSi and HBOT is a potential strategy for glioma therapy (Xie et al., 2018); there is no conclusive evidence for the use of HBOT for prevention or management of head and neck cancer (Sultan et al., 2017); the efficacy of advanced wound care and HBOT utilization in the management of hypoxic wounds was noted (Griffiths et al., 2018); and further research is necessary to assess the effect of HBOT in leukemia. Nevertheless we are recopilating further data on HBOT therapy that seems to favor its use in cancer as an adjuvant therapy.

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Citation: Michael J. Gonzalez, Manish KC et.al, "Research advances in hyperbaric oxygen therapy use in cancer: A Review". American Research Journal of Oncology , Volume 3, Issue No. 1, 2021, pp. 1-6.