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REVIEW ARTICLE

Hyperbaric oxygen and radiation therapy: a review

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Abstract
About 5% of cancer patients treated with radiotherapy will have severe late-onset toxicity. Hyperbaric oxygen therapy (HBOT) has been used as a treatment for radiation injuries for decades, with many publications presenting data from small series or individual cases. Moreover, we know that the hypoxic areas of tumours are more resistant to radiation. HBOT increases the oxygen tension in tissues and, theoretically, it should enhance the efficiency of radiotherapy. To better understand how HBOT works, we carried out this bibliographic review. We found Grade B and C evidence that at pressures exceeding 2 absolute atmospheres (ata), HBOT reduced late-onset radiation injuries to the head and neck, bone, prostate and bladder. It also appeared to prevent osteoradionecrosis after exodontia in irradiated areas. Finally, HBOT at 2 ata increased the effectiveness of radiation in head and neck tumours and achieved promising results in the local control of high-grade gliomas.

Keywords Hyperbaric oxygen therapy · Radiotoxicity · Radio-sensitization · Cancer

The use of hyperbaric oxygen therapy in the treatment of toxicity and radio-sensitization: myths and realities

There are a wide range of situations that can benefit from hyperbaric oxygen therapy (HBOT). The common denominator in all of them is tissue hypoxia in which the oxygen supply or its use is reduced or insufficient. HBOT is a non-invasive technique which aims to achieve high oxygen partial pressures in tissues by allowing the patient breathe pure oxygen at higher than atmospheric pressure inside a pressurized cabin. Depending on the therapeutic intention and the severity of the lesions, HBOT usually uses treatment pressures between 2.0 and 2.5 absolute atmospheres (ata) for periods from 60 to 120 min, once a day for a total of 30–60 sessions.

Concurrently, there is ample evidence for the beneficial effects of radiotherapy (RT) in the treatment of malignancies. Physicians are increasingly using more conformed RT techniques such intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). These therapies allow the delivery of a high dose of RT to a very specific area and limit the irradiation of healthy tissues. However, despite these technological advances, their effectiveness in hypoperfused tissues has not increased. This may be because these tissues contain hypocellular, hypovascular, and hypoxic areas which have lost the capacity for self-repair and have an intrinsic resistance to radiation.

HBOT causes a series of physiological effects as a result of increased plasma oxygen transport and better tissue availability [1]. The high oxygen gradient that this technique creates between neighbouring healthy tissues and irradiated tumours influences angiogenesis and stimulates microvascularization and neocollagenization. The mechanism of action of HBOT was initially explained by the combination of the solumetric and volumetric effects of breathing pure oxygen inside a pressurised cabin. That is, the sum of high dissolved oxygen tension in the plasma as well as its greater availability to tissues.

Measurement of tissue oxygen using transcutaneous oximetry ($TcpO_2$) has shown that the oxygen tissue tension of irradiated tissues recovers after only 8 sessions of HBOT. After this point, a plateau is reached in the progression curve, with $TcpO_2$ values of 80–85% compared to healthy non-irradiated tissues. These values are maintained for a minimum of 3 years, without the continued need for HBOT [2]. Svalestad

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[3] observed an increase in vascular and lymphatic density in biopsies from previously irradiated tissues after 20–40 HBOT sessions, thus confirming findings that had been described 30 years earlier [2].

The high oxygen tension that induces the repair of necrotic tissues and wound healing through angiogenesis and the formation of a collagen matrix, also has the ability to increase oxidative stress and the production of free radicals. We know that this imbalance in the appearance of free radicals is involved in the genesis of multiple diseases [4]. This apparent contradiction produced controversy, which was reflected in several publications. While some warned of the risks of an imbalance in the production of free radicals, others argued that HBOT corrected this balance by producing endogenous antioxidants and therefore, did not increase systemic oxidative stress [5, 6].

In 1994, Rodbell and Gillman shared the Nobel Prize for Medicine and Physiology for their discovery of G proteins and the role they play in the transmission of signals in cells [7]. This led to renewed interest in this field of investigation which showed that reactive oxygen and nitrogen species (RONS) are really 'signal transducers' that activate various growth factors, cytokines, and hormones in a cascade, meaning that oxidative stress is not synonymous with oxygen toxicity [8].

Moreover, the complete sequencing of the human genome is now available, making it possible to use DNA microarrays to evaluate the qualitative and quantitative effects of HBOT on the expression of certain genes. By noting how the use of different pressures selectively affects certain genes, we can now clarify the pressures and times required to obtain certain beneficial effects and, therefore, learn how to reduce the severity of radio-induced lesions [9, 10].

The complications of HBOT are related to the difficulty of balancing the pressure in the ears and sinuses of patients. The most frequent and specific side effect is transient myopization, which is reversible over a few months [11] and mostly affects patients who receive treatments longer than 4 weeks. There is also a small risk (1/10,000 treatments) of suffering a hyperoxic crisis, which manifests as a generalised tonic–clonic seizure and rarely leaves sequelae. However, the predisposing factors for this secondary effect are unknown. Absolute contraindications for the application of HBOT are claustrophobia, untreated pneumothorax, and heart failure with an ejection fraction $\leq$ 30 to 35%, although other situations also require caution during the use of this therapy.

Potential for use of hyperbaric oxygen therapy in late-onset complications from radiotherapy

In Spain, approximately 50% of patients diagnosed with cancer will receive radiation as an integral part of their treatment; less than 5% of these present severe late-onset toxicity. This complication can appear after a period of a few or many years, but significantly impacts patient quality of life.

HBOT has been used in this field since the 1980 s. However, the number of patients who have access to these treatments is limited given the meagre availability of facilities with multiplace hyperbaric chambers capable of reaching working pressures exceeding 2 ata (only 17 were associated with hospital centres in Spain at the time of writing). In addition, because the standard protocols currently used last between 6 and 8 weeks, the patient 'rotation' rate is 5 patients/place/year, meaning that places are available for 40 patients/year in a standard 8-seat multiplace chamber.

The beneficial effect of HBOT for the treatment of mandibular osteoradionecrosis was described from the beginning of the use of this technique [12]. Similarly, the application of this therapy as prophylaxis for pre- and post-manipulation complications of irradiated bone or soft tissue (for example, dental extractions [13] or plastic surgery operations on previously irradiated tissues [14]) was also established early on. HBOT was also found to be particularly useful in patients with radio-induced cystitis—a very disabling complication.

A study on the cost-effectiveness of the technique in radio-induced lesions concluded that 83% of patients treated with HBOT presented objective or complete improvement, and put the incremental cost-effectiveness ratio at €4013/success [15]. These rates reached 89% in the case of patients affected by radio-induced cystopathy and/or haemorrhagic proctopathy, corresponding to a ratio of €4476/success.

Considering the fact that incremental cost-effectiveness ratios below € 5000/success are very favourable, and that these do not include the collateral economic benefits of reducing the use of opioids and other drugs, as well as the rates of readmissions, blood transfusions, and surgeries, HBOT would be a treatment to take into account for the majority of patients with radiation toxicity, especially if more conventional treatments do not work.

It is also worth mentioning 'low-pressure fabric hyperbaric chambers', made with plasticised fabrics and limited to pressures of 1.4 ata (0.4 bar). However, as stated by the Undersea and Hyperbaric Medical Society, these are fed with oxygen compressors that do not reach the concentration or pressure required to achieve a radio-sensitizing and/or therapeutic effect [16].

The start of radio-induced lesion treatments with hyperbaric oxygen therapy in Spain

In Spain, the use of HBOT in the treatment of radio-induced injuries began less than 40 years ago, with the pioneering Hospital de Caridad in Cartagena and Hospital de la Cruz Roja in Barcelona. In line with most European countries, and unlike the US, Spain opted for multiplace hyperbaric chambers installed in hospital centres, which offer safety and

quality standards which are unattainable in single-seat chambers. In the latter, the patient is alone and isolated inside the chamber. Furthermore, single-seat chambers pressurise with oxygen, while multiplace pressurisation is carried out with compressed air which is far less risky.

Current recommendations for hyperbaric oxygen therapy for the treatment of toxicity

Although HBOT has been used to treat late-onset RT injuries since 1975, most published studies have reported small data series or individual case reports, as the one appeared in 2007 that enrolled 65 patients with chronic radiation enteritis treated with HBO between 1991 and 2003. Although findings suggested that HBO2 results in clinically significant improvement in two-thirds of patients [17], no much more literature about chronic radiation enteritis has been published since then.

Only a few comparative studies or quantitative systematic reviews are available. In 2001, the European Society for Therapeutic Radiology and Oncology and the European Committee for Hyperbaric Medicine drew up a consensus document [18] with the aim of confirming the positive effect of HBOT on osteonecrosis of the jaw and radiation cystitis, as well as to encourage the completion of future clinical trials in this field.

The jaw is an endochondral ossification bone which is poorly vascularised. In addition, after irradiation, it is frequently exposed by spontaneous ulcerations of the oral mucosa secondary to hyposalivation or reduced saliva secretion from the irradiated salivary glands. Exposure of the bone carries a high risk of infection, which causes osteitis that can rapidly evolve into a pathological jaw fracture; these often become externally fistulised with a consequently devastating impact on patient quality of life.

Radio-induced haemorrhagic cystitis causes pathologies ranging from occasional haematuria to persistent anaemia and even unstoppable haematuria whose treatment requires techniques that are difficult in irradiated patients such as embolization of hypogastric arteries or cystectomy. This pathology causes a notable deterioration in patient quality of life because of pain and an increased urination frequency in addition to the haematuria. HBOT has been shown to be effective in reducing haematuria and its accompanying symptoms [15], but is not the therapy of choice in patients with a grade 4 SOMA/LENT score and uncontrollable haematuria [19].

The consensus proposals were considered and are reflected in the 14 trials on the use of HBOT to improve radio-induced injuries and prevent surgical complications that were included in the 2016 Cochrane review [20]. This review concluded that there was moderate evidence for the efficacy of HBOT to restore mucosal coverage and prevent complications during reconstructive surgery for osteoradionecrosis. It also showed potential efficacy in the treatment of radio-induced proctopathy and cystopathy as well as improved post-surgical evolution after the placement of cover flaps in irradiated areas, hemimandibulectomy, and healing of the dental alveoli after tooth extractions. No conclusions about gastrointestinal radiation injury were included.

The 10th European Consensus Conference on Hyperbaric Medicine [21] established the following consensus-based recommendations:

Type 1 recommendation with B-level evidence

- Prevention of osteoradionecrosis after tooth extractions.
- Osteoradionecrosis of the jaw.
- Soft tissue radionecrosis (cystitis or proctitis).

Type 2 recommendation with C-level evidence

- Osteoradionecrosis of other bones.
- Prevention of the loss of osseointegrated implants in irradiated jaws.
- Soft tissue radiation in other locations, especially in the head and neck.
- Surgery on irradiated areas.

Type 3 recommendation with C-level evidence

- Treatment or prevention of radio-induced lesions in the larynx.
- Radio-induced CNS lesions.

Hyperbaric oxygen therapy and tumour radio-sensitization

Physical evidence justifying its use

The antitumour effect of ionising radiation is based on the damage it causes to the DNA of neoplastic cells, either directly (35%) or indirectly (65%) [22]. The latter is the most important, given the production of free radicals that fix radio-induced damage when in the presence of oxygen. In anoxic conditions, the dose must be increased by an oxygen enhancement ratio (OER) factor of 2.5–3 to obtain the same effect as that produced in the presence of oxygen [23]. These data are crucial, because a partial pressure difference of 40–60 mm versus 8–10 mm for normal and tumour tissues has been demonstrated. Tumour hypoxia is multifactorial because it involves alterations in perfusion, diffusion, and chronic anaemia.

There is also a second biological concept that supports its use, because hypoxia induces transcription factors involved

in tumour progression. One of these, *HIF-1* (*Hypoxia Inducible Factor-1*), regulates microRNAs involved in tumourigenesis, angiogenesis, metabolism, apoptosis, proliferation, metastasis, and is involved in treatment resistance. Responding elements are present in the promoter regions of these genes that can be linked by the α and β subunits of *HIF1*, thus inducing their transcription. Furthermore, once binding is established, the transcription product usually stabilises *HIF1* by forming positive feedback loops [24]. However, *HIF1*-inducible microRNAs (the most studied of which is *miR-155* [25]) have also been found that trigger negative feedback after a prolonged period of hypoxia, which therefore decrease *HIF1* levels.

MDR1 stands out from among the genes transcribed as a result of *HIF-1*; this gene causes multidrug resistance to cytotoxic agents and its expression in hepatocarcinoma (HPC) confers resistance to 5- fluorouracil (Adrucil) [26]. Another study revealed that the deletion of *miR-210* radiosensitizes HPC cells, inhibiting their proliferation and promoting apoptosis [27]. And they could allow to improve the knowledge of the physiopathology of the hyperbaric oxygen at tumoral level, because it is possible to determine them in the plasma.

Radio-sensitization with hyperbaric oxygen therapy

Oxygen is an essential element in cellular response to radiation [28, 29]. In vitro studies resulted in a leap forward in our knowledge of the implications of oxygen in radio-sensitivity. Numerous publications have demonstrated, either through histopathological studies or direct measurements of oxygen tension and the localisation of hypoxic areas using imaging techniques, that tumours have hypoxic zones that confer them an increased intrinsic resistance to radiation. This resistance is considered one of the main causes of tumour control failure [30]. It is also responsible for the lack of efficacy of various chemotherapeutic agents.

Gray [31] found that hypoxia limited the response to irradiation in rodents, and showed that the use of HBOT increased radio-sensitivity by increasing the oxygen tension in hypoxic tumour cells, leading to an intensification of the effect of the irradiation [32]. In 1957, a clinical trial was carried out in which HBOT was administered simultaneously with RT (using a modified hyperbaric chamber) in a total of 35 patients with breast or lung cancer, with favourable evolution data for the hyperoxygenated patients [32]. However, the excessive toxicity reported by Churchill [33] when HBOT was used with hypofractionated RT schemes, as well as unfavourable evolutionary parameters such as increased metastasis and the appearance of secondary tumours, caused its use as a radio-sensitizer to be relegated.

However, at the end of the twentieth century, new work appeared in favour of the use of HBOT. In Japan [34], the use of HBOT in the treatment of brain gliomas after they had been irradiated produced promising results. A British study [35] found increased overall survival (OS) in patients treated with HBOT in two trials with head and neck tumours and in another trial this therapy produced better local control (LC) and progression-free survival (PFS) results [36].

More recently, the COST (European Cooperation in Science and Technology) organisation financed the COST B-14 project [37] with three clear development and application objectives: the creation of an updated computer access network for its members, protocols for the application of HBOT, and proposals for future lines of research. These approaches focused on brain tissue and head and neck tumours because these both develop from non-vascular epithelium and grow in a hypoxic environment that promotes the maintenance of clonogenicity.

At the beginning of this century, there was a renewed interest in radio-sensitization, particularly in brain gliomas [38]; with the knowledge that the presence of sufficiently high tissue oxygen tensions allowed RT to be administered immediately after patients left the hyperbaric chamber, making it possible to use conventional fractionation for these tumour types and thus, avoiding problems such as prophylactic myringotomy, sedation, and toxicity from the simultaneous administration of both techniques. Finally, the work of Kinoshita [39] determined that the optimal time to administer RT after sensitisation was during the first 15 min after the oxygen therapy session.

Recent scientific evidence

In 2007, Overgaard [40] published a systematic review of the effect of hypoxia on radiation treatment. This analysis included 86 randomised trials with a total of 10,108 patients and showed that correction of tumour hypoxia improved the effect of RT, with an OR of 0.77 (95% CI, [0.71–0.86]) in head and neck and uterine cervix tumours locorregional control (LRC) and OR of 0.86 (95% CI, [0.76–0.98]) in neck tumours OS, without an increased risk of complications. When various methods of modifying oxygenation were evaluated, HBOT proved to be the most effective from among them. Most of the studies carried out since then have focused on locations previously proposed by COST B-14, preferably glioblastomas and squamous cell carcinomas of the head and neck.

Brain tumours

Ogawa [41] published the interim results of a phase II trial evaluating the efficacy and toxicity of concomitant chemoradiation therapy applied 15 min after HBOT in high-grade gliomas; 41 patients were treated with a total dose of 60 Gy with conventional fractionation and they obtained a response

in 57% with a mean of 12.3 months to progression and an OS of 17.3 months. Of these, 10% had temporary G4 haematological toxicity (leukopenia and thrombopenia). The results were later updated with a longer follow-up [42] which showed an OS of 20.2 months, and notably, no evidence for greater toxicity with the use of HBOT. Similar conclusions in terms of toxicity and disease control were reported in reviews by other authors [43, 44].

In work published by Yahara [45], efficacy and adverse effects were studied in a sample of 24 patients diagnosed with glioblastoma and treated with IMRT-SIB (simultaneous integrated boost) 10 min after administering hyperbaric oxygen. The OS and PFS at 2 years were 46.5% and 35.4%, respectively, and the toxicity was mild and comparable to that obtained with conventional fractionation. Koshi [46] analysed the impact of OHB and SBRT in patients with recurrence of previously treated high-grade gliomas, reporting a mean OS of 19 months. Seven of these tumours were subsequently resected and one of them showed no tumour viability.

Finally, in terms of brain metastases treated with HBOT, Hartford [47] irradiated 26 lesions with SBRT after HBOT in 18 patients. Their preliminary results after a median follow-up of 13.3 months showed an OS and LC of 71% and 100%, respectively. However, they have not yet published toxicity data because the trial (NCT01850563) is ongoing.

In an in vitro study (intracranial xenograft of glioma U87-luciferase in male mice), Clarke [48] postulated that the efficacy of RT would increase after a transient increase in tissue oxygenation, even if the tumour tissue oxygenation returns to its previous level of hypoxia, because this increased efficacy is mediated, in part, by *HIF1*-dependent mechanisms. Moreover, although HBOT seems to improve the general response to RT or chemotherapy, it should not be used as an exclusive treatment because one article reported that it promoted tumour growth in an experimental animal model [49].

Head and neck tumours

A Cochrane systematic review [50] found an improvement in LC immediately after irradiation with a relative risk (RR) of 0.58 (95% CI [0.39–0.85], with moderate quality evidence because of imprecise results), as well as lower local recurrence at 5 years with a RR of 0.77 (95% CI [0.62–0.95], moderate quality evidence because of inconsistency between trials). Of note, the patient risk of death also reduced at 1 year (RR: 0.83, CI [0.70–0.98]) and 5 years (RR: 0.82, 95% CI [0.69–0.98]). The evidence for the former was high; in the latter case a sub-analysis suggested that the benefit of HBOT was limited to patients who had received ≤ 12 RT fractions compared to those who received conventional fractionation (RR ≤ 12 fractions: 0.96, 95% CI [0.75–1.22] vs. RR for > 12 fractions: 0.69, 95% CI [0.53–0.89]).

No trials had recorded patient quality of life, and all the benefits obtained with HBOT appeared to be at the cost of an increased risk of local adverse effects (RR: 2.64, 95% CI [1.65–4.23], high-quality evidence).

However, it is worth highlighting that the studies reporting mortality at 5 years included in this review were from 1973 to 1999, with the fractionations, equipment, dosimetry, and technology of those years, far away of 3DRT and current technology and treatment schedules. [51].

Cervical tumours

The same Cochrane review concluded that no clear benefits were obtained in cervical tumours treated with HBOT in terms of local recurrence (RR 1 year: 0.82, 95% CI [0.63-1.06], high evidence; and RR 5 years: 0.85, 95% CI [0.65–1.13], moderate quality evidence caused by inconsistency between trials) or in the rate of metastasis development at 2 years (RR: 1.05, 95% CI [0.84–1.31], high evidence) and 5 years (RR: 0.79, 95% CI [0.50–1.26], moderate quality evidence caused by inconsistency between trials) [49]. No clear benefit was obtained in terms of 1-year or 5-year mortality (RR 1 year: 0.88, 95% CI [0.69–1.11], high evidence; RR 5 years: 0.95, 95% CI [0.80–1.14], moderate quality evidence because of inconsistency between trials). Regarding the increase in adverse effects appearing after HBOT, the risk of serious injury during treatment was 2.05 (95% CI [1.22–3.46], high evidence). No trials had recorded patient quality of life or seizure-risk data during HBOT treatment.

Bladder tumours

There was no benefit to HBOT in patients with bladder tumours in terms of the risk of developing metastases at 2 years (RR: 2.0, 95% CI [0.58–6.91], moderate quality evidence because of inconsistency between trials) or in as a decrease in 1-year mortality (RR: 0.97, 95% CI [0.74–1.27], high-level evidence). No trials had reported data on LC failure, local recurrence, quality of life, or adverse effects.

All types of cancer

Analysis of all the tumour types together showed evidence for an increased risk of serious radiation-related tissue toxicity after the use of HBOT (RR: 2.35, 95% CI [1.66–3.33], high-quality evidence), with a consequent increase in seizures (RR with HBOT: 6.76, 95% CI [1.16–39.31], moderate quality evidence because of imprecision).

Conclusions

There is moderate evidence that, when used at adequate pressures (exceeding 2 ata), HBOT reduces late-onset radiation tissue injury to bone, head and neck soft tissue, prostate, and bladder. Likewise, it seems to prevent the development of osteoradionecrosis after exodontia or extraction of dental root remains in a previously irradiated area. Therefore, in our opinion, this technique should be included in our arsenal of reparative or palliative treatments for radiation-generated toxicity and used in isolation or in combination with other medical or surgical procedures.

Likewise, the currently available scientific evidence from studies conducted at pressures exceeding 2 ata, indicates that HBOT could increase the therapeutic efficacy of RT in head and neck tumours (expecting encouraging results in high-grade gliomas), at the expense of greater toxicity. The optimal moment for sensitisation is reached within the first 15 min after oxygenation, not within the first half hour, as hypothesized in the 1970s.

In these previous studies, the procedure involved very primitive RT hypofractionation schemes (e.g. a total dose delivered in only six fractions), and so we could expect that, with current IMRT techniques and/or dynamic 3D-CRT, administered with HBOT in the optimal order, this toxicity could be reduced while still maintaining the observed favourable effects. Furthermore, thanks to our improved understanding of molecular biology, we now know the scientific reasoning behind these events.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflicts of interest.

Ethical statements This was an observational study. The Research Ethics Committee at the Castellón Provincial Hospital Consortium confirmed that no ethical approval was required for the completion of this work.

Informed consent As a review article, no individual patient information or images were collected. Therefore, written informed consentswere not required.

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