Hyperbaric oxygen therapy in fibromyalgia and the diseases involving the central nervous system

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ABSTRACT

Objective. *This paper briefly describes the therapeutic mechanisms underlying hyperbaric oxygen therapy (HBOT), and reviews data concerning its effects and efficacy in Parkinson's disease (PD) and fibromyalgia (FM).*

Methods. *The studies included in this review all evaluated the effect of HBOT in patients with diseases involving CNS. The PubMed databases were searched from 1980 to September 2019 using the keywords: 'hyperbaric oxygen therapy', 'fibromyalgia' and 'Parkinson's disease'.*

Results. *HBOT is already indicated in various diseases and is the subject of continuous research and development. Data from models of PD show that it may play a neuroprotective role because of its ability to reduce oxidative stress and neurodegeneration, and protect against neuronal apoptosis. It is effective in improving the symptoms and quality of life of fibromyalgia patients, and rectifies abnormal brain activity in pain-related areas. Evidence from animal studies supports its use as an alternative treatment for other rheumatic diseases as it alleviates pain and reduces inflammation.*

Conclusion. *Data mainly from animal studies support the use of HBOT in the treatment of PD and rheumatic diseases, but further work is necessary to clarify its therapeutic role in patients with these chronic disorders.*

Introduction

The concept of hyperbaric oxygen therapy (HBOT) can be traced back to 1662, but it was not actually used as a therapy until 1943. It has been the world's standard for the treatment of decompression sickness among military and commercial divers and aviator since 1967 (1). Over the past 20 years, it has been used to treat more than 100 disorders worldwide despite the insufficient scientific evidence regarding its benefit and safety (2). There is now growing interest in its possible use to treat neurodegenerative diseases such as Parkinson's disease (PD), as well as fibromyalgia (FM) (3, 4), because satisfying results are not always achieved with pharmacological and non-pharmacological therapies currently used to treat these conditions.

The aim of this narrative review is to describe the mechanisms underlying HBOT, and summarise the available data concerning its effects and efficacy in PD and FM.

Principles of hyperbaric oxygen therapy

HBOT is defined by the Undersea and Hyperbaric Medical Society (UHMS) as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurised to above sea level pressure (1 atmosphere absolute, 1 ATA = 760 mmHg) (5). It is carried out in a monoplace (for a single person) or multiplace chamber (typically for 2–14 patients). Treatment sessions are usually 30-120 minutes long, depending on the indication, but the frequency and total number of sessions have not been standardised among hyperbaric medicine centres. Monoplace chambers are usually pressurised using pure oxygen, whereas multiplace chambers are pressurised using air and the patients breathe pure oxygen through a tight-fitting face mask, hood or endotracheal tube. The pressure usually used to treat patients (1.2–3.0 ATA) is equivalent to that experienced by a diver at an underwater depth of 5–20 metres. During treatment, arterial oxygen tension often exceeds 2,000 mmHg, and levels of 200–400 mmHg occur in tissues (6).

HBOT has mechanical and physiological effects. The former is related to Boyle's law, which states that there is an inverse relationship between pressure and volume, which explains its use in the treatment of decompression sickness and arterial gas embolism. The gas bubbles that form in a vein shrink with increasing pressure and are eliminated by collapse or expulsion from the lungs; at the same time, oxygen accelerates the dissolution of bubbles by replacing the inert gasses within them.

The physiological effects of HBOT are related to the tissue hyperoxia it gives rise to. At one atmosphere, 97% of the oxygen in arterial blood is transported with haemoglobin in erythrocytes, and the rest is transported in dissolved form in plasma. In addition to saturating haemoglobin with oxygen, HBOT increases the amount of oxygen dissolved in plasma. At 3 ATA, HBOT increases the level of oxygen dissolved in plasma from 0.3 ml/dL to 6 ml/dL (7). As tissues require 5-6 ml/dL of oxygen at rest and with good perfusion, HBOT ensures that all the oxygen required by tissues can be obtained dissolved in plasma and there is no need for the oxygen bound to haemoglobin (8). As the oxygen is in a solution, it can reach physically obstructed areas where red blood cells cannot pass, and can also enable tissue oxygenation when haemoglobin oxygen carriage is impaired, as in the case of carbon monoxide poisoning or severe anaemia.

Peripheral tissue hyperoxia promotes a number of biochemical effects that are beneficial in conditions such as infections, ischaemia and wound healing. HBOT increases the generation of oxygen free radicals, which oxidise proteins and membrane lipids, damage DNA, and inhibit bacterial metabolic functions. It is particularly effective against anaerobes, and facilitates the oxygen-dependent peroxidase system by means of which leukocytes kill bacteria (9). Furthermore, it stimulates the expression and activity of anti-oxidant enzymes in order to maintain homeostasis and the redox (reductive/oxidative) cell state, and ensure treatment safety (6). It also improves the oxygen-dependent transport of certain antibiotics across bacterial cell walls (10), and improves wound healing by amplifying oxygen gradients along the periphery of ischaemic wounds and promoting the oxygen-dependent collagen matrix formation needed for angiogenesis (11).

HBOT reduces lipid peroxidation in rats with carbon monoxide intoxication and, in ischaemic rat tissue, it reduces the leukocyte adherence and post-ischaemic vasoconstriction that normally worsen crush injuries and compartment syndromes, and cause the failure of skin flaps, grafts and reattachment procedures (12-14). Finally, it increases plasma oxygen carriage and improves micro-vascular blood flow in ischaemic tissue, thus reducing adenosine triphosphate (ATP) production and lactate accumulation (15).

The UHMS has approved the use of HBOT for 13 conditions in which its beneficial effects have been confirmed by controlled animal or clinical studies (16). It can be used as a main-line therapy in decompression sickness, arterial gas embolism, and severe carbon monoxide poisoning, and as adjunctive treatment in the case of air or gas embolism, carbon monoxide poisoning with or without cyanide poisoning, clostridial myositis and myonecrosis (gas gangrene), crush injury, compartment syndrome and other acute traumatic ischaemias, decompression sickness, arterial insufficiencies, severe anaemia, intracranial abscess, necrotising soft tissue infections, refractory osteomyelitis, delayed radiation injury (soft tissue and bony necrosis), compromised grafts and flaps, and acute thermal burn injury (16). However, it is actually used to treat more than 100 conditions worldwide even though there is insufficient scientific evidence regarding its benefit and safety (2).

HBOT is a reliable method of treatment. Most of the side effects observed during treatment are mild and reversible, although they may sometimes be very severe (17). The most frequent side effect is middle ear barotrauma, which develops when a patient's middle ear pressure cannot be equalised. The most undesirable side effect is oxygen toxicity, which is caused by the use of oxygen at higher partial pressures than those to which the body is normally exposed: this can lead to myopia due to an increase in the refractive power of the lens that resolves within weeks of completing treatment (18); it can also affect the central nervous system oxygen toxicity and give rise to epileptic episodes, but these do not cause permanent damage; and there may be lung toxicity-related coughing, chest tightening, and a temporary impairment of pulmonary function (19).

Fibromyalgia

HBOT has long been used to treat the complications of a variety of rheumatic conditions including osteonecrosis of the femoral head (29), but there is less evidence concerning its potential use as a main-line treatment of rheumatic diseases themselves.

Two studies have increased interest in its potential as a treatment for FM, a syndrome characterised by chronic widespread pain and a broad spectrum of other somatic and psychological manifestations that severely affect the patients' quality of life, including fatigue, sleep disturbances, cognitive impairment, depression, anxiety, headache, diffuse abdominal pain, and interstitial cystitis (30). It is generally considered to be the second most frequent rheumatic disorder after osteoarthritis (31), but its challenging management requires a multidisciplinary approach and even then only leads to a temporary or slight improvement in symptoms (32).

The pathogenesis of FM is still unknown, but it has been hypothesised that local hypoxia may cause degenerative changes in muscles leading to chronic pain (33), a consequent reduction in ATP and an increase of the concentration of lactic acid. In 2004, a randomised clinical trial (RCT) tested this hypothesis in 50 FM patients: 26 underwent fifteen 90-minute HBOT sessions at 2.4 ATA over three weeks, and 24 received sham treatment in the form of fifteen 90-minute sessions of breathing air at 1 ATA (34). The number of tender points, pain thresholds as measured by algometer and VAS pain scores were recorded before the first HBOT or sham session, and after the fifteenth. There

was a significant decrease in the number of tender points and pain thresholds in the HBOT group in comparison with the sham treatment group as early as after the first HBOT session that persisted until after the fifteenth session (34).

More recently, a prospective, active control, cross-over RCT evaluated the effect of HBOT on ten-der points and pain thresholds, the quality of life, and single photon emission computed tomography (SPECT) imaging of brain activity in 60 female FM patients (4). The treated group patients were evaluated at baseline and after HBOT; the patients in the crossover-control group were evaluated three times: at baseline, after a control period of no treatment, and after HBOT. After forty 90-minute sessions with 100% oxygen at 2 ATA, HBOT significantly improved all FM symptoms and the quality of life in both groups. The SPECT imaging analysis revealed the rectification of the ab-normal brain activity: reduced activity in the somatosensory cortex and enhanced activity in the frontal, cingulate, medial temporal and cerebellar cortices. These data not only show that HBOT can improve the symptoms of FM but also, and more interestingly, that it can induce neuroplasticity and significantly rectify abnormal activity in pain-related areas of the brain (4). The role of HBTO in inducing neuroplasticity in FM patients, was further supported by studies showing that the HBOT-induced clinical improvement of FM symptoms in women with history of childhood sexual abuse was associated by the improvement in brain functionality by mean of SPECT (35, 36). Furthermore, the brain microstructure analysis, made by mean of Brain Magnetic Resonance diffusion tensor imaging (MRI-DTI), showed neurogenesis in the anterior thalamic radiation, left Insula, and the right thalamus after HBOT sessions (35). The findings of these studies are in agreement with the vision of FM as "central sensitisation" a condition characterised by an abnormal pain transmission and processing within the CNS (30).

Nevertheless, although these results are encouraging, further studies are required to find the optimal dose-response curve and time of treatment. Our group (37) in a prospective, observational clinical trial involving 32 patients with FM underwent HBOT (100% oxygen at 2.5 ata with air breaks) administered on three days per week for a total of twenty 90-minute sessions for a total twenty sessions, showed in 28 patients that completed the 20 HBOT sessions that scores and the symptoms of anxiety (but not those of depression) significantly improved after both 10 and 20 sessions, whereas fatigue and FM symptom severity scores significantly improved only after 20 sessions. There was no significant change in the quality of sleep and the adverse effects were limited. Moreover, in the same population Casale *et al*. (36) carried out an observational longitudinal study focused on changes in neuromuscular efficiency (NME), which is impaired in FM and could be linked with muscle fatigue. Using electromyography (EMG), the authors demonstrated in 22 patients with FM (3M; 19F) (age 49.8±9.5; height 164.7±7.5; weight 63.8±12.7) treated with 20 sessions of HBOT at 2.4 atmosphere an increased NME but no change in EMG amplitude and muscle fibre CV. HBOT did not improve muscle strength or change muscle fibre content, but improved the ability of the central motor command to generate the same effort (MVC) with fewer recruited fibres.

Guggino *et al*. (37) based on the role of pro-inflammatory cytokines (*i.e*. IL- 1RA, IL-6, and IL-8 but not IL-5, IL-4, IL-13) in the pathogenesis of FM in a study involving 36 patients with primary FM, and 10 patients without systemic inflammatory disorders (decompression sickness, sudden and painless vision loss) (CTR HBOT) that underwent HBOT treatment enrolled as unrelated disease controls, showed a significant effect of HBOT on pain, fatigue, quality of life, mood and hours of sleep. Furthermore, by means of laboratory tests the authors reported an increase in TNF-α and IFN-γ serum levels in FM patients that correlated with disease severity. In other words, this study reported that FM patients show a T helper 1 (Th1) signature and the activation of this sub- set which is modulated by HBOT. These findings support the view that HBOT is an effective, rapid and safe means of treating various symptoms of FM. Data from inflammatory pain models show that HBOT (alone or in combination with the usual anti-inflammatory agents) may also be useful in decreasing edema and hyperalgesia (38) and, albeit with mixed results, a number of studies have investigated the effects of HBOT in rat models of induced arthritis (39-42). How HBOT favours pain relief and decreases joint inflammation in joints is still unclear (40), but it may be due to an increase in enzymatic anti-oxidant capacity favouring a decrease in lipid peroxide levels (41) or to higher oxygen pressure (42).

Very little is known about the efficacy of HBOT in other rheumatic diseases with inflammatory and autoimmune components, but it has been found that it induces changes in the CD4/CD8 ratio and decreases the proliferation of lymphocytes in rat models (41), and it reduces spontaneous immunoglobulin production, proteinuria, anti-dsDNA antibody titres, facial erythema and lymphadenopathy, improves immune-complex deposition, and increases survival in murine models of autoimmunity (44, 45).

The data concerning the use of HBOT in patients with connective tissue diseases are limited to a few case reports (46-50).

Parkinson's disease

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder, and affects 2–3% of the population aged ≥65 years. Characterised by resting tremor, rigidity and bradykinesia, its neuropathological hallmarks are neuronal loss in the substantia nigra (SN), which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of α-synuclein (20). Conventional therapy with levodopa and dopamine agonists is primarily aimed at relieving the motor symptoms, but it does not prevent dopaminergic neuron degeneration (20).

There is therefore considerable demand for new therapies that can prevent neuronal death.

The mechanisms involved in the

pathogenesis and progression of PD are not fully understood, but there is overwhelming evidence that oxidative stress, the physiological response to reactive oxygen species (ROS) production, plays a major role in dopaminergic neuronal degeneration (21). Increased ROS production and an imbalance in anti-oxidant defence and repair mechanisms lead to the loss or apoptosis of dopaminergic neurons in the SN (22), and so reversing oxidative cell damage is a rational treatment strategy (23). As mentioned above, HBOT produces oxygen free radicals and ROS, but there is increasing evidence that repeated HBOT sessions increase superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase activity, all which are enzymes that protect cells against oxidative stress (24, 25).

Therefore, the HBOT-induced enhanced formation of ROS, which results in reduced antioxidant ac-tivity, perhaps cause lipid peroxidation, organ injury, and DNA damage (26) with deleterious effects on genome, central nervous system, lung and eyes, also play a central role in coordinating cell signaling for a variety of growth factors, cytokines and hormones and for anti-oxidant, protective pathways. The ability of endogenous antioxidant responses to HBOT in improving oxidative dam-age is thought to be highly dependent on the pressure, duration, and frequency of hyperbaric oxygen exposure, as well as the metabolic health of the tissue/organism, and individual antioxidant capacity (25). However, the optimal dose and duration of HBOT is not well established, even for recognised indications. Future research is needed to evaluate the balance between the potential efficacy of HBOT in patients with PD and the possible adverse effects related to excessive production of ROS.

There is a great deal of recent evidence indicating that HBOT prevents neuronal damage and improves neurological outcomes after brain ischaemia (27). In a recent animal study of rats with 6-OHDA-induced parkinsonism, HBOT alone or in combination with Madopar (levodopa/benserazide used to treat PD) increased (1) GSH-Px and SOD activities, and reduced malondialdehyde content in the substantia nigra, an indirect sign of cell damage induced by oxygen free radicals. Furthermore, the combination treatment significantly protected against the loss of neurons positive for tyrosine hydroxylase (TH), a rate-limiting enzyme that mediates the synthesis of dopamine in the SN, and reduced the production of glial fibrillary acidic protein (GFAP), a marker of neurological damage. The levels of anti-apoptosis-related factor Bcl-2 were increased and the levels of the apoptosis-related factor Bax decreased following HBOT or the combination therapy. These findings suggest that the combined treatment plays a neuroprotective in rats with 6-OHDA-induced PD because of its ability to reduce oxidative stress and protect against Bax/Bcl-2-mediated apoptosis (3). To the best of our knowledge, there are no studies testing the effect and efficacy of HBOT in patients affected by PD. However, in the case of PD patient with severe depression and anxiety that refused to be treated with dopamine agonists or SSRIs, the most common treatments for PD patients suffering from psychiatric symptoms, HBOT for 30 days showed an improvement in scores for depression and anxiety, including Unified Parkinson's Disease Rating Scale I (UPDRS I), UPDRS II, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale. These findings suggest that HBOT may be a potential therapeutic method for PD patients suffering from depression and anxiety (28).

Conclusions

This narrative review highlights some of the beneficial effects of HBOT and the findings supporting its use for the treatment of PD and FM. Further studies are needed to improve our understanding of the mechanisms underlying the effects of HBOT and clarify its role in the treatment of these chronic disorders.

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