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Hyperbaric Oxygen Therapy in Chronic Pain Management

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Chronic pain is one of the frequently encountered clinical problems that is difficult to cure. Hyperbaric oxygen (HBO) therapy has been reported in chronic pain syndromes with promising results. In this review, we focus on the effectiveness of HBO in fibromyalgia syndrome, complex regional pain syndrome, myofascial pain syndrome, migraine, and cluster headaches. HBO may be beneficial if appropriate patients are selected. HBO is a reliable method of treatment. However, physicians performing HBO must be aware of oxygen toxicity. Another problem regarding HBO is the scarcity of centers administering it. Further research is required focusing on the optimal treatment protocol, the cost/benefit ratio, and the safety of HBO in chronic pain management.

Introduction

Pain is the most frequent symptom that causes patients to visit health institutions. Pain is a normal sensation that warns the nervous system, as the result of a chemical, thermal, or mechanical stimulus, that it needs to protect itself against a probable danger. In addition to this physiologic pain, patients also complain of pathologic pain. There are two kinds of pathologic pain: acute and chronic. Acute pain occurs immediately after illness or injury and resolves after healing. Conversely, chronic pain persists beyond the usual course of the disease and may cause intermittent or continuous pain for months to many years. Chronic pain can occur after a disease or without a known reason. The treatment of chronic pain calls for an extraordinary effort from all physicians, but satisfying results cannot be obtained in most cases. For that reason, the efficacy of several pharmacologic and nonpharmacologic methods for the treatment of chronic pain is being investigated. Many studies have been published examining the use of hyperbaric oxygen (HBO) therapy, used as an adjunct therapy in the treatment of chronic pain in recent times [1•,2•,3–8,9•,10–15]. The aim of this review is to investigate the role and effectiveness of HBO treatment as an adjunct in chronic pain management.

Principles of Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is defined as the intermittent inhalation of 100% oxygen in a hyperbaric chamber at a pressure higher than 1 absolute atmosphere (1 ATA = 760 mmHg, the normal atmospheric pressure at sea level) [16]. HBO therapy usually is administered at 1 to 3 ATA. Typically, the duration of HBO therapy varies from 30 to 120 minutes. The frequency and total number of HBO sessions are not standard among hyperbaric medicine centers. HBO therapy is administered using monoplace or multiplace chambers. In the former, a single patient is treated and internal pressure is raised with oxygen. Multiplace chambers permit patients to be in the pressure chamber together with health personnel. In multiplace chambers, pressure is raised with compressed air and patients breathe oxygen through masks.

Hyperbaric oxygen therapy causes mechanic and physiologic effects. The mechanic effects are linked to Boyle's law, which states that there is an inverse relationship between pressure and volume. Use is made of the mechanic effects of HBO in the treatment of decompression sickness and arterial gas embolism. Gas bubbles that form in the vein shrink with increasing pressure and, as a result, 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 physiologic effects of HBO are linked to the hyperoxia it gives rise to in the tissues. At one atmosphere, 97% of oxygen in the arterial blood is transported with hemoglobin in erythrocytes. The remaining oxygen is transported in dissolved form in plasma. In addition to fully saturating hemoglobin with oxygen, HBO leads to a favorable increase in the amount of oxygen dissolved in plasma. HBO at 3 ATA increases the level of oxygen dissolved in plasma from 0.3 ml/dL to 6 ml/dL [17]. At rest and with good perfusion, tissues require 5 to 6 ml/dL of oxygen. In other words, with HBO at 3

ATA, all of the oxygen required by tissues can be obtained dissolved in plasma without the need for oxygen linked to hemoglobin [18].

The Undersea and Hyperbaric Medicine Society has approved it in 13 indications demonstrated in controlled animal or clinical studies, with scientific evidence confirming that the use of HBO is beneficial [16]. Although there is insufficient scientific evidence regarding the benefit and safety of HBO, it is used for more than 100 illnesses worldwide [19]. HBO can be used as a main-line therapy in decompression sickness, arterial gas embolism, and severe carbon monoxide poisoning and as an adjunct treatment in clostridial myonecrosis, acute traumatic ischemic injury, problem wounds, osteoradionecrosis, necrotizing soft tissue infections, intracranial abscess, exceptional anemia, delayed radiation injury, thermal burns, and skin grafts and flaps [16].

Hyperbaric oxygen is a reliable method of treatment. Most side effects observed during treatment are slight and reversible, although these side effects may be very severe at times [20]. The most common side effect is middle ear barotrauma, which develops when patients' middle ear pressure cannot be equalized. The most undesirable side effect of HBO therapy is oxygen toxicity caused by the use of high levels of oxygen. Reversible myopia forms with toxic effects on the lens and resolves within weeks after the completion of treatment [21]. Central nervous system oxygen toxicity and epileptic episodes may be observed, but these do not cause permanent damage. Pulmonary toxicity-related coughing, chest tightening, and temporary impairment of pulmonary functions may be seen [22].

The Use of Hyperbaric Oxygen in Fibromyalgia Syndrome

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disorder characterized by widespread pain and exquisite tenderness at specific anatomic sites (ie, tender points) [23]. There is a global decrease in pressure pain thresholds rather than specific changes limited to the tender points [24]. The etiopathology of FMS is still unknown, although it is thought that the disease is caused by several interacting factors such as muscle overload, poor posture of the spine, disturbed sleep, psychogenic factors, local hypoxia, and reduced concentrations of high-energy phosphate [25]. However, it is thought that local hypoxia can lead to degenerative changes in the muscles of patients with FMS [25]. Studies on the role played in FMS pains by local hypoxia are along the lines that there is local hypoxia at tender points, that total mean oxygen pressure is lower in FMS patients' subcutaneous tissues compared with those of control subjects, that there is vasoconstriction in the skin tissue beneath tender points, that capillary density is lower in muscle tissue, and that muscular blood flow is at a lower level.

When the circulation is compromised, the resultant ischemia lowers the concentration of adenosine triphosphate (ATP) and increases the concentration of lactic acid. Increased oxygen delivery to the tissue with HBO may prevent tissue damage in ischemic tissues by decreasing the tissue lactic acid concentration and helping maintain the ATP level. HBO therapy causes hyperoxia by raising oxygen concentration far above physiologic levels in all tissues during treatment. This breaks the hypoxia-pain vicious circle in FMS patients.

A randomized, controlled study was performed on 50 FMS patients in our clinic, with 26 patients being classified as the HBO group and 24 analyzed as the control group. The patients with FMS in the HBO group were given 15 90-minute sessions at 2.4 ATA over 5 days, and patients in the control group breathed air for 90 minutes at 1 ATA. At the end of the study, the number of tender points in patients, visual analogue scale (VAS) score, and pain thresholds were used in evaluation. The number of tender points in patients with FMS who received 15 HBO sessions declined, VAS scores decreased, and there was a statistically significant increase in pain thresholds. In these patients, it was thought that the effect of HBO treatment overcame local hypoxia, which is regarded as present in the painful points in FMS patients, by establishing hyperoxia in the entire body. Thus, the pain-hypoxia vicious circle was broken with HBO treatment and pain decreased significantly [1•].

In one pain study performed on the pain intensity of patients with fibromyalgia, pain was shown to increase with nitric oxide (NO) synthesis [26]. We think that there is a reduction in pain intensity through a reduction in the NO effect with HBO therapy. It again was shown in a new study that NO plays a role in hyperoxic vasoconstriction [27]. HBO therapy reduces regional blood flow by lowering the NO level in the brain. It is thought that HBO acts by reducing the NO effect in FMS.

Our study demonstrated HBO as a beneficial method in FMS; however, multi-institutional, prospective, randomized, controlled studies are needed. In addition, further studies should address the effect of inhalation of 100% oxygen at 1 ATA in FMS.

The Use of Hyperbaric Oxygen in Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is characterized by pain in the extremities, changes in skin color, hypo- or hyperhydrosis, and localized osteoporosis [28]. It is thought that excessive sympathetic nervous system activity plays a major role in its pathology. Early diagnosis influences response to treatment and the course of the illness. In the first stage of the disease, immediately following arteriovenular bed and capillary vessel pressure vasodilatation, an intense pain and reddening accompanied by a feeling of burning develops with edema and

hyperesthesia in the skin. The second phase can be distinguished approximately 3 months later as vasoconstrictive phenomena enter the equation with the dystrophic evolution of the skin and nearby tissues, the lower skin, and even the muscles, tendons, ligaments, and bone. The third phase constitutes the irreversible stage of the disease. In this phase, vasomotor pains and complaints appear and trophic changes in the skin-muscle-skeleton structure assume a permanent and heavier state, until the emergence of ankylosis and loss of functional capacity.

The hypoxia and acidosis that emerge during CRPS increase the sensation of pain and reduce pain tolerance. With HBO therapy, the hyperoxia forming in the body leads to vasoconstriction, lowers edema, and raises tissue partial oxygen pressure. Moreover, it stimulates the depressed osteoblast activity and reduces the formation of fibrous tissue.

Tuter et al. [3] applied HBO therapy to 20 of 35 patients and combined analgesic treatment to 15. A clear reduction in pain intensity was observed in CRPS patients receiving HBO therapy. Peach [4] reported in a case study that pain disappeared following one session of HBO therapy in a patient who was allergic to steroids, nonsteroidal anti-inflammatory drugs, and narcotic analgesics. In a placebo-controlled, randomized study that included 71 CRPS patients in our clinic, 37 were administered 15 sessions of HBO therapy (90 minutes at 2.4 ATA), and 34 patients were given placebo treatment (air for 90 minutes at 2.4 ATA). All of the patients were examined after the first and fifteenth sessions and on day 45. A clear reduction in pain and edema was determined in those patients receiving HBO therapy. The reduction in pain again was interpreted as the antiedemic effect of hyperoxia and an increase in pain tolerance with the elimination of hypoxia [2•].

The effect of inhalation of 100% oxygen at 1 ATA on CRPS has not been studied before. Further studies should compare the effectiveness of inhalation of oxygen at 1 ATA and at 2.4 ATA in CRPS treatment.

The Use of Hyperbaric Oxygen in Myofascial Pain Syndrome

Myofascial pain syndrome (MPS) is defined as pain or autonomic phenomena referred from active trigger points, with associated dysfunction. Unfortunately, MPS often goes unrecognized, misdiagnosed, or mistreated, leading to unnecessary pain, suffering, and disability [29].

The main clinical components of MPS are trigger point taut band and local twitch responses. Trigger points play a main role in mechanisms of MPS and are easily found in the midportion or belly of the affected muscle.

The importance of these tender points is unclear, although uncontrolled studies have shown nonspecific changes of localized ischemia. The MPS paradigm varies according to its pathophysiology. Recent analyses have demolished the validity of the "spasm-pain-spasm" vicious circle. The pathophysiology of MPS is unclear, although the most reasonable definition is that given by Travell and Simons [30]. According to their model, acute muscle strain > tissue damage in a localized area of muscle > tears in sarcoplasmic reticulum > free calcium ions > sustained contraction > increased strain on vulnerable areas of muscle > free calcium ions. They proposed that free calcium ions and ATP lead to sustained contraction. This causes a hypermetabolic state locally and local vasoconstriction. Local vasoconstriction causes local ischemia, which, combined with increased energy demands, leads to some histologic changes. In addition, the tissue damage releases serotonin, histamine, and kinins, which also lead to local ischemia and nerve sensitization [30,31].

A rather wide spectrum of therapies is used in the treatment of MPS, including therapeutic ultrasonography, high-voltage galvanic currents, ischemic compression, deep-stroking massage, and dry injection. However, MAS is not encountered in the literature related to HBO.

We have administered HBO therapy (90 minutes at 2.4 ATA) to 20 MAS patients (unpublished data). Pain threshold measurements were analyzed using algometry, and pain intensity using VAS. Pain threshold increased and VAS decreased significantly after treatment compared with pre-treatment levels ($P < 0.001$). It is thought that this situation develops through the breaking of the hypoxia-membrane destabilization–pain vicious circle in the pathophysiologic mechanisms. On the other hand, it appears reasonable that high phosphate levels also are regulated with this mechanism.

Hyperbaric oxygen therapy needs to be examined in further randomized, placebo-controlled studies.

The Use of Hyperbaric Oxygen in Headaches

Headaches represent an economic burden by causing a loss of workforce and productivity. At the same time, it has a negative effect on patients' quality of life by damaging family and social relationships [32].

Most patients benefit from new pharmacologic agents. New treatment alternatives are being investigated because there may be patients whose headaches do not respond to protective treatments and pharmacologic treatments or in whom pharmacologic treatment is contraindicated (eg, patients with hypertension, peripheral vascular disease, or infections).

Normobaric oxygen (NBO) inhalation is not a new approach in the treatment of migraine and cluster headaches [33]. NBO respiration today is an accepted method in the acute treatment of cluster headaches [34]. It has been shown that oxygen relieves headache by reducing cerebral blood flow [35]. HBO increases the amount of arterial oxygen more than NBO and gives rise to more evident vasoconstriction [36•]. Therefore, it has been thought that HBO is more effective than NBO in the treatment of migraine and cluster headaches.

In addition to the vasoconstrictive effect of HBO, it also is hypothesized to contribute to a lightening of headaches by affecting neurogenic mechanisms. Di Sabato et al. [13] investigated the effect of HBO on substance P in nasal mucosa in patients with cluster headache. A reduction in immunoreactivity to substance P was observed in patients receiving HBO. Di Sabato et al. [14] also investigated serotonin bonding to mononuclear cells before and after treatment in cluster headache patients receiving HBO therapy and air therapy. A plateau was observed in serotonin bonding in patients receiving HBO. It was suggested that the serotoninergic route may play a role in the effect mechanism of HBO.

Migraine

Migraine is characterized by episodic headaches, usually affecting only one side of the head, and often accompanied by nausea, vomiting, and visual disturbances [37]. Migraine is divided into two subtypes: migraine with aura or migraine without aura. The aura, characterized by focal neurologic symptoms, may precede or accompany the attacks in migraine with aura [37]. The 1-year prevalence of migraine is approximately 18% in women, 6% in men, and 4% in children [38].

Fife and Fife [5] administered HBO therapy at varying pressures between 1.3 and 2.6 ATA to 26 patients complaining of headaches that did not respond to treatment. Full relief occurred within 16 minutes in 24 of the 26 patients. It was observed that symptoms also decreased together with headache.

Fife et al. [6] treated patients with 45-minute HBO or nitrox (10% oxygen/90% nitrogen) during migraine attacks. Pain decreased in seven of 10 patients treated with HBO and in two of four patients receiving nitrox. No statistically significant difference between the two groups was determined, but the lack of difference is related to the small size of the sample.

Myers and Myers [7] evaluated the efficacy of 100% oxygen under normobaric (1 ATA) and hyperbaric (2 ATA) conditions for a typical migraine attack. The severity of global headache was measured using a visual pain intensity descriptor scale before and after exposure to oxygen. Twenty migraine sufferers were randomly assigned to the normobaric and hyperbaric groups. All of the patients inhaled oxygen for 40 minutes in a pressure chamber. Patients were blinded to the level of pressure in the chamber. Relief was observed in only one of the 10 patients in the normobaric group, but there was an improvement in headache in nine of the 10 patients in the hyperbaric group. The difference between the groups was significant. Relief occurred in the nine patients who failed to benefit from NBO when they progressed to hyperbaric oxygen.

Wilson et al. [8] used a VAS to document relief of migraine headache after exposure to normobaric (NBO; 1.1 ATA) and hyperbaric (2.4 ATA) oxygen. They also evaluated pericranial muscle tenderness that accompanies migraine headache using manual palpation and algometry. The study protocol was designed as a prospective, randomized, double-blind, placebo-controlled study. Eight female migraine sufferers were assigned to HBO and NBO groups. Patients were taken for treatment within a maximum of 60 minutes after the migraine attacks began. HBO was administered 20 minutes after the pain passed, in such a way as not to exceed 60 minutes. NBO therapy was administered for 60 minutes. Both NBO and HBO reduced manual palpation scores; however, dolorimeter measurements after treatments were not significantly different in the two groups. In the HBO group, significant pain relief was observed after treatment, whereas NBO failed to demonstrate any improvement.

Eftedal et al. [9•] conducted a double-blinded, placebo-controlled study to determine the prophylactic role of HBO in migraine headache attacks. Patients were randomly assigned to the HBO group (100% oxygen, 20 ATA, 30 minutes) and a control group (air, 2 ATA, 30 minutes). Treatments were performed in a hyperbaric chamber for 3 consecutive days. The patients were instructed to keep a standardized migraine diary containing information regarding the number of headache attacks, their duration and intensity, accompanying symptoms, and doses of attack-averting drugs for 8 weeks before and after treatment. Mean hours of headaches per week were recorded as the efficacy parameter. Although the results indicated an initial reduction in hours of headache for the HBO group, the differences between the groups were not significant for any of the weeks.

Cluster headache

Cluster headache is characterized by attacks of extremely severe pain around and above one eye, often accompanied by at least one of the following: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, localized sweating, miosis, ptosis, and eyelid edema. These attacks last from 15 minutes to three hours, occurring as often as eight times daily [37].

Weiss et al. [10] administered HBO (2 ATA, 60 minutes) to one patient with cluster headache resistant to all treatments, including NBO inhalation. In the twentieth minute of HBO therapy, headache and nasal congestion were completely halted, but pain recurred two and a half hours later. A second HBO session was held and pain was again halted, and no further pain occurred for 7 months.

Pascual et al. [11] treated four male patients with chronic cluster headache who failed to respond to treatments with a total of 10 HBO sessions (70 minutes, 2.5 ATA) over 2 weeks. After treatment, there was a reduction in headache frequency and duration in two patients, pain frequency alone decreased in a third patient, and the last patient failed to benefit at all.

Di Sabato et al. [14] performed a placebo-controlled study on patients with chronic cluster headache. There

was no change in the number of attacks and the level of analgesic use in patients receiving environmental air treatment (placebo), whereas patients receiving HBO therapy reported a reduction in their complaints.

Di Sabato et al. [12] compared HBO and placebo therapy in the treatment of episodic cluster headache. Improvement was observed in six of seven patients in the HBO group, and in none of the patients in the placebo group. No attack was observed for 6 months in three of six patients. According to the results of this study, it is suggested that HBO was not only effective in acute attack treatment, but it also had a prophylactic effect in subsequent attacks. In addition, Nilsson Remahl et al. [15] performed a double-blinded, placebo-controlled study to investigate the efficacy of HBO in cluster headaches. Whereas one group of patients breathed 100% oxygen for 70 minutes at 2.5 ATA, the other group breathed 10% oxygen/90% nitrogen at 2.5 ATA. Treatment was administered twice, with a 24-hour interval. Patients graded their headaches from 1 to 4. A headache index (attack number X pain intensity) was calculated for each patient for 1 week before and after treatment. Patients responded to both treatments and no difference between HBO and NBO was observed.

These studies show that HBO can be an alternative method of acute treatment in patients who do not respond to other treatments, including NBO inhalation, or for whom the use of medication treatment is contraindicated. However, the optimal treatment protocol for the administration of HBO has not yet been determined. Treatment pressure, duration, and frequency vary in the published studies.

The Use of Hyperbaric Oxygen in Ischemic Leg Pain

Peripheral vascular disease (PVD) usually refers to ischemic disease of the extremities, mainly the legs. Various diseases produce ischemia of the extremities, such as arteriosclerosis obliterans, thromboangiitis obliterans, sudden embolic and thrombotic occlusion of the artery to the limb, traumatic occlusion of an extremity, and miscellaneous arteriopathies. Limb pain is the most frequent symptom of PVD.

Pain at rest is a sign of severe PVD and occurs when there is a profound reduction in the resting blood flow to the limb [39]. When HBO therapy is used in the treatment of PVD-related wounds, relief in ischemic leg pain is observed frequently. However, few publications on this subject were found. Urayama et al. [40] reported relief of rest pain in five of the six patients suffering from chronic occlusive disease in the lower extremities. It has been proposed that action mechanisms of HBO are relief of hypoxia and edema, decreased accumulation of algogenic polypeptides, and increased affinity of endorphins for receptor sites [39].

Vascular surgery is the first choice in PVD treatment. HBO may be promising as an adjunct to medical treatment in patients who are not suitable for vascular surgery.

Conclusions

Hyperbaric oxygen is a promising treatment modality in chronic pain management. Physicians dealing with chronic pain syndromes must consider HBO when conventional treatments fail. Further studies must be performed to determine the optimal treatment protocol, the cost/benefit ratio, and the safety of HBO in chronic pain management.

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