Pain management and hyperbaric oxygen therapy

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Chronic pain is very common in the general population. Hyperbaric oxygen therapy has been studied in various chronic pain syndromes, including fibromyalgia syndrome, complex regional pain syndrome, myofascial pain syndrome, migraine and cluster headaches. Although the results of these studies are promising, routine management of these chronic pain syndromes with hyperbaric oxygen therapy cannot be justified at this time. However, hyperbaric oxygen therapy may be used in selected patients unresponsive to other treatments, where facilities are available, after carefully weighing potential benefits against the risks of treatment. Further large-scale, good-quality, randomized, controlled studies are required to clearly demonstrate efficiency, cost–effectiveness, optimal treatment protocol and safety of hyperbaric oxygen therapy in the management of chronic pain.

The most frequent symptom leading to applications to health institutions is pain [1]. Pain is a crucial physiological sensation, since it gives warning to the nervous system that it must protect itself against a probable danger as the result of a chemical, thermal or mechanical stimulus. However, pathological pain may be a symptom of a disease when it is acute or turn into a distinct phenomenon when it becomes chronic, leading to intermittent or continuous pain for several months or years [2]. The prevalence of chronic pain in the general population is very high [3]. The effectiveness of various pharmacological and nonpharmacological methods of treating chronic pain is under investigation, since no completely satisfactory results have been obtained [4]. There are an increasing number of articles studying hyperbaric oxygen therapy (HBOT) as an adjunct in the treatment of various chronic pain syndromes [5–19]. The aim of this article is to highlight the role and effectiveness of HBOT in the management of chronic pain.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is defined as the inhalation of 100% oxygen intermittently in a hyperbaric chamber at a pressure higher than 1 atmosphere absolute (ATA; 1 ATA = 760 mmHg, which is the normal atmospheric pressure at sea level) [20]. HBOT is usually administered at 2–3 ATA and the duration of HBOT varies from 60 to 300 min, depending on the indication [20]. The frequency and total number of HBOT sessions are not standard among hyperbaric medicine centers.

HBOT causes mechanical and physiological effects. Its mechanical effects emerge as a result of the inverse proportion between pressure and volume as a requirement of Boyle's law. This effect is used in the treatment of decompression sickness and arterial gas embolism. The physiological effects of HBOT are related to the hyperoxia it establishes in the tissues. HBO at 3 ATA increases the level of oxygen dissolved in plasma from 0.3 to 6 ml/dl [21]. At rest and with good perfusion, tissues require 5–6 ml/dl of oxygen. Therefore, with HBOT at 3 ATA, all the oxygen required by the tissues can reach them dissolved in plasma, without the need for oxygen attached to hemoglobin [22].

HBOT exerts different biochemical and cellular effects. By providing adequate oxygen tension, HBOT increases collagen synthesis, maturation and fibroblast proliferation and promotes angiogenesis and wound healing in hypoxic wounds [23]. HBOT reduces leukocyte adhesion in reperfusion injury, preventing release of proteases and free radicals that cause vasoconstriction and cellular damage [24]. HBOT augments oxygen-dependent killing of organisms by polymorphonuclear leukocytes [25]. In addition, HBOT is bactericidal for anerobes such as *Clostridium perfiringens* and inhibits production of clostridial α-toxin [26,27]. Although HBOT reduces regional blood flow by hyperoxia-induced vasoconstriction, resultant oxygen tension is hyperoxic owing to the increased oxygen content of the blood [28].

The Undersea and Hyperbaric Medicine Society has confirmed 13 indications with proven scientific evidence, controlled animal or clinical

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studies or demonstrated with broad clinical experience in which the use of HBOT is beneficial (**Box 1**) [20]. However, HBOT is employed in the treatment of more than 100 diseases worldwide, despite the lack of adequate scientific proof of benefit, or even safety, in these conditions [29].

HBOT is a reliable treatment method [21,30]. Most of the side effects observed during treatment are slight and reversible; however, occassionally they may be very severe [31]. The most frequently observed side effect is middle-ear barotrauma [31]. Reversible myopia arises due to toxic effects on the lens and resolves within weeks after the completion of treatment [32]. CNS oxygen toxicity and epileptic seizures may be observed, although these do not cause permanent damage [33]. Pulmonary toxicity-induced coughing, tightening of the chest and temporary impairment in pulmonary functions may be observed [34].

HBO in fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disorder characterized by diffuse pain and exquisite tenderness at specific anatomical sites (i.e., tender points) [35]. Although the etiopathogenesis of FMS remains unclear, several etiological factors have been proposed, including muscle abnormalities, disturbed sleep, physiological disorders and neuroendocrinological changes [36].

It has been hypothesized that degenerative changes in the muscles of patients with FMS are the result of reduced blood flow and local hypoxia [37]. When the circulation is compromised, the resultant ischemia reduces the concentration of ATP and increases that of lactic acid [38]. Increased oxygen delivery to the tissues with HBO may prevent tissue damage in ischemic tissues by reducing the tissue lactic acid concentration and helping maintain the ATP level. Based on this hypothesis, Yildiz and colleagues conducted a controlled, randomized study to evaluate the efficiency of HBOT in FMS [5]. A total of 50 patients with FMS who had persistent symptoms in spite of medical and physical therapy were randomly assigned to a HBO group (n = 26) and a control group (n = 24). The HBO group received a total of 15, 90-min sessions of HBOT at 2.4 ATA over 3 weeks, while the control group inhaled air for 90 min at 1 ATA inside the hyperbaric chamber. Patients abstained from medical and physical therapy during the study period. The number of tender points in patients, visual analog scale (VAS) pain scores and pain thresholds on the tender points were assessed before and after the study. Evaluations were made in a blinded fashion. In the HBO group, the number of tender points and VAS pain scores decreased and pain thresholds were increased significantly after HBOT. However, in the control group, none of the parameters improved after treatment. The mechanism of beneficial effects of HBOT in FMS is not clear. It can be proposed that HBOT reduced pain in tender points by eliminating local hypoxia in the muscle tissue. However, recent studies challenge the hypothesis that hypoxia is a contributing factor in the pathogenesis of FMS [39]. Therefore, other mechanisms are likely to be involved in the beneficial effects of HBOT in this disorder.

Although Yildiz and colleagues demonstrated the beneficial effects of HBOT in FMS [5], large-scale studies are needed to confirm their findings. In addition, further studies should address the effect of inhalation of 100% oxygen at 1 ATA in FMS.

HBO in complex regional pain syndrome

Complex regional pain syndrome (CRPS) is characterized by pain in the extremities, hyperesthesia and localized autonomic dysfunction following injury to soft tissue or nerve [1]. The pain is usually associated with changes in skin color and temperature, hypo- or hyperhydrosis and edema [40].

Since the outcomes of recent strategies for CRPS treatment are not satisfactory, novel treatments are continually being investigated [41]. In a

Box 1. Indications of hyperbaric oxygen therapy approved by the Undersea and Hyperbaric Medicine Society [20].

Main treatment

- Air or gas embolism
- Carbon monoxide/cyanide poisoning
- Decompression sickness

Adjunctive treatment

- Enhancement of healing in selected problem wounds
- Compromised skin grafts and flaps
- Clostridial myositis and myonecrosis (gas gangrene)
- Refractory osteomyelitis
- Necrotizing soft-tissue infections
- Crush injury, compartment syndrome and other acute traumatic ischemic injuries
- Soft tissue/bone radiation necrosis
- Exceptional blood loss (anemia)
- Intracranial abscess
- Thermal burns

placebo-controlled, randomized study, Kiralp and colleagues evaluated the efficiency of HBOT in patients with CRPS [6]. A total of 71 patients diagnosed with CRPS were randomly allocated to HBO (n = 37) and a control group (n = 34). Patients in both groups received 15, 90-min therapy sessions with either 100% oxygen (HBO group) or normal air (control group) at 2.4 ATA on 5 days of the week (one session/day). During the study, no physical therapy, except paracetamol (3 × 500 mg/day), was administered to patients. Patients were evaluated before treatment, after completion of the 15 sessions and after 45 days. The evaluating physician was blinded to the patient groups. HBOT decreased pain and wrist edema and increased wrist mobility. However, hyperbaric air failed to demonstrate any benefit. The beneficial effects of HBOT may be ascribed to decreased edema due to hyperoxic vasoconstriction [42,43], in addition, to stimulation of depressed osteoblast activity and reduction of fibrous tissue formation [44].

Previous reports also demonstrated beneficial effects of HBOT in CRPS. Tuter and colleagues administered HBOT and caffetin preparation to 35 patients with CRPS [7]. They reported that both treatments decreased pain significantly. However, while the efficiency of caffetin was restricted by the time of its administration, the efficiency of HBOT persisted during 6 months in 87% of the patients. In a case report, Peach and colleagues reported that pain disappeared after one session of HBO in a patient with CRPS allergic to steroids, nonsteroidal anti-inflammatory drugs and narcotic analgesics [8].

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

HBO in myofascial pain syndrome

Myofascial pain syndrome (MPS) is characterized by trigger points of pain and/or autonomic phenomena referred from active trigger points, with associated dysfunction [45]. Trigger points are located in a taut band, a palpable ropy thickening of the muscle tissue [46]. Simple pressure on the trigger points produces referred pain to areas overlying or distant to the tenderness and a local twitch response [46].

The pathophysiology of MPS is unclear. A muscle lesion resulting from an acute trauma or repetitive microtrauma leads to the rupture of the sarcoplasmic reticulum and the release of calcium from intracellular stores. The calcium build-up causes persistent muscle contraction, which leads to ischemia by compressing local blood vessels and increasing metabolic demands. This oxygen/nutrient deficit results in a rapid depletion of local ATP. As a result of the hypoxia-induced drop in ATP concentrations, the function of the calcium pump in the muscle cell is impaired, and the sarcoplasmic calcium concentration remains elevated, which increases muscle contractile activity – a vicious cycle [47].

A number of therapies were employed in the treatment of MPS, with varying success [47]. HBO has also been investigated in the treatment of MPS due to the presence of local ischemia in its etiology [48]. Kiralp and colleagues administered a total of ten sessions of HBOT (90 min at 2.4 ATA) to 20 patients with MPS in 2 weeks [Kiralp MZ *et al.* Unpublished Data]. Pre- and post-treatment comparisons revealed that pain thresholds increased and VAS pain scores decreased significantly with HBOT. It is thought that this is due to the breaking of the hypoxia membrane destabilization–pain cycle of pathophysiological mechanisms by increasing oxygen availability in the muscle tissue. Conversely, high phosphate levels regulated by this mechanism also appear reasonable. However, owing to the lack of a control group, efficacy of HBO in the treatment of MPS has not yet been conclusively proven.

HBO in pain associated with peripheral vascular disease

Peripheral vascular disease (PVD) usually refers to ischemic disease of the extremities, particularly the legs. 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 [49].

HBOT is used frequently in the treatment of chronic wounds in patients with PVD. Together with the improvement in wound healing, extremity pain is also relieved with HBOT. In a double-blind, randomized, prospective study of 65 patients with atherosclerotic occlusive disease, Kovacevic and colleagues determined a significant increase in pain-free walking distance in 3 months in 35 patients who were administered HBOT [50]. Uruyama and colleagues reported pain relief in five out of six patients with chronic PVD who received HBOT [51].

The postulated benefits of HBOT include relief of hypoxia and edema, decreased accumulation of algogenic polypeptides and increased affinity of endorphins for receptor sites [49]. It is likely that HBOT reduces pain associated with

PVD by improving the underlying condition. However, the use of HBOT in the treatment of ischemic leg pain cannot be recommended at this time. More clinical research and further controlled studies are required.

HBO in headaches

Headache is one of the most frequent clinical problems in medicine [52]. Although new pharmacological agents are highly effective in headache management [53,54], new treatment alternatives are needed for patients not responding to preventive treatments or in whom pharmacological treatment is contraindicated (patients with hypertension, PVD or infections) [55]. The vast majority of headaches are not the result of any structural disturbances. These headaches are defined as primary headaches, and include migraine, tension-type headaches and cluster headaches [56].

Migraine

Migraine is defined as an episodic headache, usually affecting only one side of the head and often accompanied by nausea, vomiting and visual disturbances [57]. The 1-year prevalence of migraine is approximately 18% in women, 6% in men and 4% in children [58].

The efficiency of HBOT in migraine attacks was evaluated in three randomized, controlled studies. In a small study, Fife and colleagues compared the efficiency of 100% oxygen (HBO group) and nitrox (10% oxygen/90% nitrogen mixture) at 2 ATA for 45 min in patients with migraine [10]. Pain decreased in seven out of ten patients treated with HBO and in two out of four patients receiving nitrox. Myers and Myers evaluated the efficacy of normobaric oxygen (NBO; 100% oxygen at 1 ATA) and HBOT (100% oxygen at 2 ATA) for a typical migraine attack by measuring pain intensity with a visual pain intensity descriptor scale before and after exposure [11]. All patients inhaled oxygen for 40 min in a pressure chamber. Patients were blinded to the level of pressure in the chamber. Pain relief was observed in nine out of ten patients in the HBO group and one out of ten in the NBO group. Wilson and colleagues used a VAS to document the relief of migraine headache after exposure to NBO (1.1 ATA) and hyperbaric (2.4 ATA) oxygen [12]. Eight female migraine sufferers were assigned to HBO and NBO groups. Patients were taken for treatment within a maximum of 60 min after the migraine attacks began. In the HBO group, significant pain relief was observed after treatment, while NBO failed to demonstrate any improvement. It has been shown that oxygen relieves headache by reducing cerebral blood flow [59]. HBO increases the level of arterial oxygen greater than NBO and gives rise to more evident vasoconstriction [55]. Therefore, it is hoped that HBO will be more effective than NBO in the treatment of migraine.

The ability of HBOT to reduce the frequency of migraine attacks was investigated by Eftedal and colleagues in a double-blind, placebo-controlled study [13]. Patients received either HBOT (100% oxygen, 2 ATA, 30 min) or placebo therapy (air, 2 ATA, 30 min) for 3 consecutive days. Patients were instructed to keep a standardized migraine diary 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.

In their case series, Fife and Fife administered HBOT at different pressures (1.3–2.6 ATA) to 26 patients whose headaches were unresponsive to a variety of therapies. They observed complete relief of headache in 24 (92%) patients [9].

Cluster headache

Cluster headache is characterized by attacks of extremely severe pain around and above one eye, often accompanied by conjunctival injection, lacrimation, nasal congestion, rhinorrhea, localized sweating, miosis, pitosis and eyelid edema [57].

Pure oxygen inhalation is not a new approach in the treatment of headaches [60]. Furthermore, currently, oxygen inhalation is an accepted method of acute treatment of cluster headaches [61]. Case reports by Weiss and colleagues and Pascual and colleagues demonstrated positive effects of HBOT on patients with cluster headaches resistant to all treatments [14,15]. They also reported that HBOT reduced the number of subsequent attacks [14,15]. Di Sabato and colleagues conducted placebo-controlled studies to assess the efficacy of HBOT in cluster headache and to demonstrate the mechanism of action [16–18]. Improvement was observed in patients receiving HBOT, while patients in the placebo group failed to improve [18]. They suggested that HBO was not only effective in acute attacks but that it also had a prophylactic effect in subsequent attacks [16]. Di Sabato and colleagues demonstrated a reduction in immunoreactivity to substance P in nasal mucosa of

patients receiving HBOT [17]. They also observed investigated serotonin bonding to mononuclear cells in patients receiving HBOT. A plateau was observed in serotonin bonding in patients receiving HBO. It was suggested that the serotoninergic route might play a role in the mechanism of action of HBOT [18].

Although Di Saboto and colleagues reported the superiority of HBOT over placebo, a recent study failed to concur. Nilsson-Remahl and colleagues administered HBOT (100% oxygen at 2.5 ATA) and placebo therapy (10% oxygen/90% nitrogen at 2.5 ATA) to patients with cluster headache [19]. They calculated a headache index (attack number × pain intensity) for each patient before and after treatment. They concluded that there was no difference between HBOT and placebo therapy, and that both were efficacious.

HBOT can be an alternative method of acute treatment in patients who do not respond to other treatments, including NBO inhalation, or in whom the use of medication treatment is contraindicated. However, the low number of subjects studied reduces the scientific validity of the results. In addition, treatment pressure, duration and frequency of HBOT vary in the published studies. Further large-scale, high-quality studies are required to delineate the role of HBOT in the treatment of headaches.

Expert commentary & outlook

In this report, we have reviewed the studies dealing with the use of HBOT in different chronic pain conditions, including FMS, CRPS, MPS, pain associated with PVD and headache. Although the results of controlled studies are promising, there is much work to be performed before the general use of HBOT is recommended in these conditions. The number of randomized controlled studies is very low, and the scientific quality of these studies is questionable. However, we believe that HBOT can be used in patients whose symptoms are unresponsive to other treatments after carefully weighing up the potential benefits and risks of the treatment.

The low number of HBO facilities is an important weakness of HBOT. NBO can be easily administered even in a primary medical institution. Further studies should compare the effectiveness of HBOT and NBO inhalation in FMS, CRPS and MPS.

HBOT is a reliable method of treatment and may find a constant place in the management of chronic pain in the future. We hope that the results of the studies reviewed in this report encourage clinicians to conduct well-organized, controlled studies to identify the effectiveness, cost:benefit ratio and safety of HBOT, and define an optimal treatment protocol for its administration in the management of patients with chronic pain.

Highlights

- Hyperbaric oxygen therapy (HBOT) may be an alternative therapeutic method in the management of chronic pain.
- HBOT reduces pain in fibromyalgia and complex regional pain syndrome.
- HBOT halts migraine and cluster headache attacks.
- HBOT has a prophylactic effect on cluster headache attacks.
- The use of HBOT in the management of chronic pain is still experimental.

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