The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases

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ABSTRACT: Hyperbaric oxygen therapy (HBOT) has been investigated as a primary/adjunctive treatment for a number of injuries and medical conditions including traumatic ischemia, necrotizing soft tissue injuries, non-healing ulcers and osteoradionecrosis, but the results are controversial. There is insufficient evidence to support or reject the use of HBOT to quicken healing or to treat the established non-union of fractures. However, in patients with fibromyalgia, HBOT reduces brain activity in the posterior cortex and increases it in the frontal, cingulate, medial temporal and cerebellar cortices, thus leading to beneficial changes in brain areas that are known to function abnormally. Moreover, the amelioration of pain induced by HBOT significantly decreases the consumption of analgesic medications. In addition, HBOT has anti-inflammatory and oxygenatory effects in patients with primary or secondary vasculitis. This review analyzes the efficacy and limitations of HBOT in orthopedic and rheumatologic patients.

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The Undersea and Hyperbaric Medicine Society (UHMS) defines hyperbaric oxygen therapy as, "an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute [ata])" [1]. Hyperbaric oxygen therapy (HBOT) increases hemoglobin saturation and leads to a tenfold to twentyfold increase in the amount of oxygen dissolved in blood plasma, which is more available to tissues than oxygenated hemoglobin, and makes it possible to deliver greatly increased partial oxygen pressure to tissues. It can be delivered in a high-pressure multi-place, high-pressure mono-place, or low-pressure mono-place chambers. For clinical purposes, the pressure must be ≥ 1.4 ata, and typically involves pressurization to between 1.5 and 3.0 ata for periods of 60–120 minutes one or more times daily. The use of HBOT can be traced to the 1600s. The first well-known chamber was built and run by a British clergyman named Henshaw in 1662, but it was not until 1917 that German inventors Bernhard and Heinrich Dräger successfully applied pressurized oxygen to treat decompression illness due to diving accidents. Decompression sickness remained the only indication for a long time, but HBOT has more recently been investigated as a primary or adjunctive treatment for a number of injuries and medical conditions, including traumatic ischemia, necrotizing soft tissue injuries, non-healing ulcers, and osteoradionecrosis. The UHMS and European Consensus Conference have periodically updated the indications [2]. The last revision included 14 indications [Table 1].

The aim of this article is to analyze the evidence of the efficacy of HBOT in orthopedics and rheumatological diseases.

METHODS

We searched the MEDLINE database (PubMed, National Library of Medicine, Bethesda, MD, USA) and used combinations of the key words "hyperbaric oxygen therapy," "ulcers," "vasculitis," "fractures," "rheumatologic(al) diseases," "pain," and "fibromyalgia." The reference lists of all of the selected articles were also scanned for references not identified in the initial search. We limited our search to citations from January 1990 to December 2016.

HBOT AND FRACTURES

The treatment of fractures is intended to re-establish the structural integrity of a fractured bone and restore function to the injured body part; however, the process of fracture healing is sometimes impaired and leads to delayed union or, in some cases, hypervascular (hypertrophic) or avascular (atrophic) non-union (i.e., no healing 6 months after the injury), which often require

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Table 1. Undersea and Hyperbaric Medicine Society's indications for HBOT [2]

• Arterial air or gas embolism
• Acute decompression illness
• Acute carbon monoxide poisoning/carbon monoxide poisoning complicated by cyanide poisoning
• Necrotising soft tissue infections
• Acute thermal burns
• Crush injury, compartment syndrome, other traumatic ischemias
• Gas gangrene (clostridial myonecrosis)
• Compromised graft or flap preservation
• Arterial insufficiency: central renal artery occlusion, to enhance healing of selected problem wounds
• Intracranial abscesses
• Severe anemia
• Chronic refractory osteomyelitis
• Osteoradionecrosis, soft tissue radiation necrosis
• Sudden idiopathic sensorineural hearing loss

further in-patient care and, in many cases, multiple surgeries and prolonged rehabilitation. Animal studies have shown that HBOT increases bone generation and the removal of dead bone but, although there have been reports of clinical improvements in patients with established non-union fractures, the evidence supporting its effectiveness in treating non-healing fractures is still weak [3,4]. HBOT has been used to treat crush injuries and compartment syndromes in a limited number of centers around the world, and is often recommended in the hyperbaric medicine literature [5,6]. A wide range of animal models of soft tissue flap ischemia have demonstrated the ability of HBOT to preserve acutely ischemic tissue and improve flap survival, and others have demonstrated substantially accelerated and qualitatively better healing of muscles, tendons, peripheral nerves and bone [7-11].

Hyperbaric oxygen therapy (HBOT) has been investigated as a primary/adjunctive treatment for a number of injuries and medical conditions, but the results are controversial

HBOT can significantly reduce post-trauma edema and moderate inflammatory processes, as well as up-regulate various endogenous antioxidant systems [12]. During or immediately after ischemia, it can inhibit ischemia-reperfusion injuries via mechanisms that include the inhibition of β2 integrin-mediated neutrophil adhesion during reflow [12]. It also accelerates angiogenesis and fibroblast function to increase the healing of problematic wounds [13]. Two randomized, controlled trials have shown that HBOT improves arterial flow and local skin perfusion, increases the rate of complete healing, and reduces the need for further surgery compared to standard treatment, but they did not report any functional measures or long-term outcomes [14,15].

The still ongoing Hyperbaric Oxygen for Lower Limb Trauma (HOLLT) study is an international, multi-center, open-label, randomized trial involving patients with crush injuries that caused complex fractures in the lower leg [16]. Patients with an acute, open fracture of the tibia and severe soft tissue injury (Gustilo grade 3) were randomized to a standard surgical protocol with or without HBOT in the acute phase (within 48 hours of injury). HBOT was administered in 90 minute sessions at 2.4 ata twice daily for the first 3 days, and then once daily until reaching a total of at least 12 sessions. The primary aim of the study was to evaluate the incidence of acute fracture wound complications, defined as the occurrence of significant soft tissue necrosis developing after initial surgery and/or significant wound infection within 2 weeks of the injury. The early secondary outcomes (14 days after injury) that were measured included the date, time and nature of all operative procedures; the length of stay in the intensive care unit; and the length of acute hospitalization. The late secondary outcomes (3–24 months after injury) that were assessed included the occurrence of soft tissue infection, osteomyelitis, any other wound complications, whether the patient was able to bear his or her weight on the injured leg, and the number and nature of any other surgical procedures required [16]. The results have yet to be published. There is currently insufficient evidence to support or reject the use of HBOT as a means of accelerating the healing of acute injuries or treating established non-union fractures. However, all of the results and actions of HBOT are attractive in setting of orthopedic, soft tissue traumas, and, we believe, in facial traumas involving the mandible. The mandible is frequently injured after facial trauma, and the condyle is involved in about 25–40% of mandibular fractures [17]. The management of mandibular condylar fractures (MCFs) is still controversial [18]. A recent meta-analysis showed that, compared to closed treatment, open reduction and rigid internal fixation (ORIF) leads to better functional and clinical outcomes, including a maximal inter-incisal opening, latero-protrusive movement, protrusive movement, malocclusion, and reduction of pain and chin deviation on mouth opening [19]. However, it is contraindicated for the management of bilateral intracapsular condylar head fractures because of the high risk of avascular necrosis and the associated loss of functioning condyle, the possible development of fibrous or osseous ankylosis, and the subsequent need to remove loose hardware [20]. Active mandibular movement is particularly important in preventing ankylosing, avascular necrosis and the loss of functioning condyles in this highly vascularized and osteogenic environment [18]. Given these data we treated a patient with a diagnosis of bilateral compound multi-fragmented intracapsular fractures of the mandibular condylar heads by means of computed tomography (CT) with a total of 80 HBOT sessions, combined with physiotherapy and opening exercises for about 12 months (2–3 sessions/week with an exceptional improvement in the signs and symptoms of MCF confirmed by magnetic resonance imaging (MRI) [unpublished data]. We suggest

that HBOT, combined with early and aggressive physiotherapy, had a beneficial effect on bilateral MCF, particularly because it acted on capsular elasticity, although it did not lead to the disappearance of bone dislocations revealed by MRI. Furthermore, HBOT combined with early and aggressive physiotherapy can have a beneficial effect on fractures by reducing the complications of the orthopedic injuries and preventing the fibroses adhesions induced by the aggressive physiotherapy [13]. It can also improve clinical outcomes such as acute and chronic pain because of the immediate and prolonged release of nitric oxide and endogenous nitric oxide opioids counteracting abnormal brain pain processing [21,22].

In conclusion our current understanding of HBOT is that it can reduce the complications of orthopedic injuries and thus improve outcomes [13]. It is hoped that the results of the HOLLT study, case reports and future trials will provide new data about the usefulness of HBOT in these types of injuries.

HBOT AND PAIN

CHRONIC PAIN AND DYSFUNCTIONAL SYNDROMES

The management of chronic pain is sometimes challenging and requires a multidisciplinary approach. Most pharmacological and physical therapies only slightly or temporarily ameliorate pain symptoms, and often they have adverse effects that interfere with the patient's quality of life and lead to non-adherence [23]. The analgesic effects of HBOT have been studied in nociceptive, inflammatory and neuropathic pain models, and may be useful for the treatment of various chronic pain syndromes [21,22].

HBOT has shown that it inhibits nociception in murine models of pain, an effect that is probably mediated by the neural nitric oxide-dependent release of opioid peptides [21]. This effect acts centrally but also involves the release of neuronal dynorphins and the activation of μ- and *k*-opioid receptors in the spinal cord [22]. HBOT may also play a role in inhibiting the inflammatory response following injury and the associated inflammatory pain, as it has been shown to be as effective as aspirin in decreasing inflammation and mechanical hypersensitivity in a rat model of arthritis [24].

In patients with fibromyalgia, hyperbaric oxygen therapy (HBOT) led to beneficial changes in brain areas that are known to function abnormally and to ameliorate pain

Promising results have been obtained in animal models of neuropathic pain treated with HBOT. Gu and colleagues [25] found that daily treatment at 3.0 ata for 7 days starting 30 minutes after chronic constriction-induced sciatic nerve injury reduced the severity and duration of thermal hyperalgesia and mechanical allodynia in rats, both of which are behavioral indicators of neuropathic pain. This effect has been associated with decreased production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β [26], changes in the phosphorylation of proteins thought to be involved in the development of neuropathic pain such as NMDA receptors, and decreased expression of spinal neuronal NOS (nNOS) and inducible NOS (iNOS) [27].

The clinical usefulness of HBOT in treating different types of human pain has been investigated in conditions such as chronic headache, complex regional pain syndrome, trigeminal neuralgia, and fibromyalgia. Five randomized, controlled trials have shown that HBOT has some efficacy in treating acute migraine attacks but not in preventing future attacks [28], and various authors have found that it can be effective in treating and preventing cluster headache [29]. However, as the methodological quality of all of these studies was moderate to low, and they were underpowered because of the small number of patients, further studies of larger patient series with more robust design are required.

HBOT has led to promising results in complex regional pain syndrome, and the findings of one small trial suggest that it may also be useful in treating idiopathic trigeminal neuralgia [28].

FIBROMYALGIA AND CHRONIC FATIGUE

Fibromyalgia syndrome is one of the most common causes of chronic widespread pain. It is characterized by reduced pain thresholds (hyperalgesia) and pain with normally innocuous stimuli (allodynia) [30]. Fibromyalgia is common, with a prevalence of 2% in the general population. However, its diagnosis and management remain a challenge for patients and healthcare professionals. The diagnosis of fibromyalgia often takes more than 2 years with an average of 3.7 consultations with different physicians [30]. Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common. Patients with fibromyalgia have a diverse combination and varying severity of these symptoms. Co-morbidities, especially depression and anxiety, are also common but not universal in all patients. Therefore, fibromyalgia is a heterogeneous and complex condition. The quality of life in almost all of the patients with fibromyalgia syndrome is reduced. Both impaired physical functions and emotional impact adversely affect the quality of life of fibromyalgia patients. Approximately 50% of all the patients have difficulty with routine daily activities while 30–40% have to stop work or change their employment. The societal cost of fibromyalgia due to reduced productivity is high. As fibromyalgia is a complex syndrome associated with a wide range of symptoms, treatment should be tailored to the individual, addressing their particular needs and targeting their most distressing symptoms. The best strategy is to use a multidisciplinary approach to treatment, using both pharmacological and non-pharmacological interventions as required [31]. Non-pharmacological treatments that have been tested in fibromyalgia syndrome include: exercise, cognitive behavioral therapy, homeopathy, physiotherapy, acupuncture, magnetism,

dietary alterations and laser therapy [31]. These interventions are generally safe and therefore long-term use is not detrimental. Excessive pain in fibromyalgia may be due to hyper-excitability of the pain processing pathways and under-activity of the pain inhibiting pathways in the brain. Comparisons of single-photon emission computed tomography (SPECT) findings in fibromyalgia patients and healthy subjects revealed high levels of activity in the somatosensory cortex and reduced activity in the frontal, cingulate, medial temporal and cerebellar cortices [32]. It has been shown that HBOT increases cell metabolism, reduces apoptosis, alleviates oxidative stress, and increases neurotrophin and nitric oxide levels by enhancing mitochondrial function in neurons and glial cells, and it may even promote the neurogenesis of endogenous neural stem cells [33]. HBOT-induced neuroplasticity also leads to the repair of chronically impaired brain functions in patients who have experienced a stroke or mild traumatic brain injury with prolonged post-concussion syndrome. Furthermore, there is a body of evidence supporting the use of HBOT to decrease inflammation and pain behaviors in rodents, but there is a lack of evidence concerning its clinical usefulness in human pain conditions. However, Yildiz et al. [34] found that HBOT significant reduced the number and threshold of tender points, and an Israeli group [35] evaluated its efficacy in improving the symptoms of fibromyalgia patients by rectifying their typically altered brain functions. The study endpoints included a tender point count, pain threshold measurements, functional impairment, and brain activity as assessed by means of SPECT. HBOT led to a statistically significant improvement in the mean dolorimeter threshold and the number of tender points; furthermore, it reduced brain activity in the posterior cortex and increased activity in the frontal, cingulate, medial temporal and cerebellar cortices, thus leading to beneficial changes in the activity of specific brain areas whose functions are known to be abnormal in fibromyalgia patients. Furthermore, the post-HBOT amelioration of pain levels led to a significant decrease in the consumption of analgesic medications [36].

The efficacy of HBOT has recently been studied in patients with chronic fatigue syndrome (CFS), a chronic disease with social effects due to the subject's inability to fulfill their work, social and family responsibilities. In a small study of 16 patients, Akarsu and colleagues [36] found that HBOT decreased the severity of symptoms and increased the patient's quality of life. However, further studies are needed to confirm this efficacy in fibromyalgia and CFS patients.

HBOT IN SECONDARY AND PRIMARY VASCULITIS

The prevalence of chronic leg ulcers in patients with an underlying rheumatologic disease is reported to range from 5.6% in patients with systemic lupus erythematosus (SLE) to about 9% in patients with RA. In the majority of cases, the etiology was vasculitis, but other causes included venous disease, peripheral artery disease, and granulomatous dermatitis. In a retrospective review by Chia and Tang [37] regarding the outcomes of chronic leg ulcers in patients with rheumatologic diseases (RA, SLE, overlap syndromes, systemic sclerosis and ankylosing spondylitis), 15 of the 29 patients with leg ulcers had a diagnosis of RA, 8 had a diagnosis of SLE, 3 were diagnosed with overlap syndromes, 1 with systemic sclerosis, and 1 with ankylosing spondylitis. In the majority of cases, the patients required an addition or change in immunosuppressive agents and/or compression therapy, but four patients underwent HBOT due to no beneficial response to other treatment options. Furthermore, HBOT has recently been used to treat ulcers in systemic sclerosis patients failing to respond to conventional therapies with promising results.

Systemic vasculitides are a frequent cause of non-healing skin ulcers, which have a significant impact on co-morbidity, mortality and therapeutic costs. By altering local hypoxic conditions, HBOT can facilitate wound-healing and energy-consumption processes. Moreover, hyperoxia has an anti-inflammatory effect on the vascular bed. HBOT has long been used in addition to antibiotics, debridement and revascularisation in the treatment of chronic non-healing wounds associated with diabetes or non-diabetic vascular insufficiency, but its use in conditions, such as vasculitides, is still under debate [2]. In 2006, Efrati and co-authors [38] published an interesting study on the use of HBOT in 35 patients with vasculitis-induced severe ulcers, which did not heal despite intense immunosuppressive treatment. The baseline treatment protocol consisted of the administration of 100% O_2 at a pressure of 2 ata for 90 minutes five times a week for 4 weeks. Additional sessions were planned in selected cases. After HBOT, 28 patients (80%) showed complete healing and four showed partial healing; only three patients did not respond, and none of the patients experienced any HBOT-related side effects. Ulcer tissue oxygenation was evaluated by measuring transcutaneous oxygen pressure ($TcPO_2$) using a pulse oximeter before and after HBOT. There was a significant increase in $TcPO_2$ after HBOT, which explains the high response rate. Interestingly, no significant differences in baseline characteristics or tissue oxygenation were observed between the non-responders and the patients whose wounds completely healed. It is therefore difficult to predict who will benefit from HBOT, and further studies are needed for clarification.

Hyperbaric oxygen therapy (HBOT) has anti-inflammatory and oxygenatory effects in patients with primary or secondary vasculitis

Hyperbaric oxygenation at 2–2.5 ata fully oxygenates hemoglobin, and the amount of dissolved oxygen in plasma increases more than tenfold, thus exceeding tissue oxygen requirements. HBOT therefore generates a positive gradient for oxygen diffusion from functioning capillaries to ischemic tissue sites and, by altering conditions of local hypoxia, facilitates wound-healing

processes such as fibroblast proliferation or angiogenesis. Furthermore, it has a beneficial effect on non-ischemic ulcers, possibly because of its anti-inflammatory action. A number of animal models have shown that HBOT inhibits vascular inflammatory responses by reducing the rolling and adhesion of neutrophils in the micro-circulation of the brain, liver, skeletal muscles and bowel [12,13]. It has also been shown to enhance plasma anti-oxidant defenses, and may contribute to angiogenesis and regulate vascular tone by stimulating vascular endothelial growth factor and interleukin 6 release and decreasing endothelin-1, thus ultimately fostering wound healing [12,13]. Its efficacy has been investigated in various conditions, but the evidence for most is scant even though a recent Cochrane review has reported the short-term benefits of HBOT in the healing of diabetic foot ulcers. Therefore, no definite conclusions can be drawn concerning its effects on chronic wound healing with other underlying etiologies [39].

OSTEONECROSIS

Few studies of HBOT as joint-preserving treatment for symptomatic early-stage osteonecrosis of the femoral head have been published. However a study reviewed the files of 68 patients who were treated with HBOT. The study comprised 78 symptomatic joints diagnosed with Steinberg stage I and II osteonecrosis by means of MRI [40]. At the time of follow-up, 93% of the joints survived. Mean Modified Harris Hip Score and Short Form-12 health survey (SF-12) improved from 21 to 81 ($P < 0.0001$). The mean physical component of the SF-12 questionnaires showed improvement from 24 to 46 ($P < 0.0001$), and the mean mental component of the SF-12 improved from 54 to 59 ($P < .0001$) [40].

The cellular and molecular mechanism through which HBOT improves osteonecrosis remains unclear. However, the data from a basic study showed that HBOT has a direct suppressive effect on osteoclast differentiation and activity in normoxic and hypoxic conditions. This result would appear to be associated with a reduced response to the receptor activator of nuclear factor kappa-B ligand (RANKL) and secondary to changes in *HIF*, *RANK*, and *NFATc1* gene expression. This result suggests that the beneficial effects of adjunctive HBOT on necrotic bone may occur in part due to a reduction in aberrant osteoclast activity [3].

These data suggest that HBOT is effective in osteonecrosis, although further studies are needed to confirm these clinical and basic findings.

LIMITATIONS ON THE USE OF HBOT IN CLINICAL PRACTICE

One limitation of HBOT is the risk of adverse effects, including pressure-induced damage to the ears, sinuses and lungs lasting from 1 day to 2 weeks, temporary worsening of myopia for several weeks, and claustrophobia during therapy. Oxygen poisoning may manifest itself acutely as a neurological event (often acute), but only a problem during therapy), or it may accumulate slowly and decrease respiratory function. It is also necessary to take into account the high costs of the technique.

CONCLUSIONS

Future research should concentrate on identifying which patients can benefit from HBOT, defining the optimal time for the intervention, and drawing up specific dose-response curves for each condition. However, this type of evaluation may be complicated for at least two reasons. First, the optimal dose and duration of HBOT is not well established, even for recognized indications. Second, patient blinding may be a problem as there cannot be any true placebo condition, although it may be possible to use a short exposure vs. high pressure at the beginning of a session to replicate the sensation of HBOT. However, this modification may lead to short periods of increased plasma oxygen partial pressure (i.e., short period of increased plasma oxygen) affecting the results. Nevertheless, there is a real need for more adequately powered trials designed to minimize all kinds of bias and to establish the appropriate indications for HBOT, both in orthopedic and rheumatologic conditions.

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Capsule

Bioresorbable scaffolds versus metallic stents in routine PCI

Bioresorbable vascular scaffolds were developed to overcome the shortcomings of drug-eluting stents in percutaneous coronary intervention (PCI). Wykrzykowska et al. performed an investigator-initiated, randomized trial to compare an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent in the context of routine clinical practice. The authors randomly assigned 1845 patients undergoing PCI to receive either a bioresorbable vascular scaffold (924 patients) or a metallic stent (921 patients). The primary endpoint was target-vessel failure (a composite of cardiac death, target-vessel myocardial infarction, or target-vessel revascularization). The median follow-up was 707 days. Target-vessel failure occurred in 105 patients in the scaffold group and in 94 patients in the stent group (2 year cumulative event rates 11.7% and 10.7%, respectively, hazard ratio [HR], 1.12, 95% confidence interval [CI], 0.85–1.48, $P = 0.43$); event rates were based on Kaplan–Meier estimates in time-to-event analyses. Cardiac death occurred in 18 patients in the scaffold group and in 23 patients in the stent group (2-year cumulative event rates 2.0% and 2.7%, respectively), target-vessel myocardial infarction occurred in 48 patients in the scaffold group and in 30 patients in the stent group (2 year cumulative event rates 5.5% and 3.2%, respectively), and target-vessel revascularization occurred in 76 patients in the scaffold group and in 65 patients in the stent group (2 year cumulative event rates 8.7% and 7.5%, respectively). Definite or probable device thrombosis occurred in 31 patients in the scaffold group as compared with 8 patients in the stent group (2 year cumulative event rates, 3.5% vs. 0.9%, HR 3.87, 95%CI 1.78–8.42, $P < 0.001$).

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