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The Effects of Hyperbaric Oxygen Therapy in Treatment on Diverse Diseases

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ABSTRACT

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) indeed holds significant therapeutic potential across various medical conditions, primarily by increasing the concentration of oxygen delivered to tissues under pressure. Saturating tissues with oxygen allows for the effective alleviation of underlying hypoxia, facilitating healing, tissue repair and mechanisms of action leads to reducing concentration of pro-inflammatory acute phase proteins, interleukins, and cytokines. Conversely, HBOT while also boosting levels of growth factors and other cytokines that promote angiogenesis.

REVIEW METHODS: The article was complied by analyzing data from PubMed and Google Scholar regarding effects of hyperbaric therapy.

THE STATE OF KNOWLEDGE:

Studies indicate that HBOT provides numerous opportunities in the treatment of extensive diseases acress various systems. Neurodegenerative disorders involve progressive nerve cell damage leading to motor or cognitive decline, exacerbated by oxidative stress and inflammation. HBOT has shown promise in delaying disease onset by improving mitochondrial dysfunction in motor neuron disease. In case of intestinal obstruction HBOT reduces intestinal gas volume, diameter of obstructed loops, and improves intestinal contractility. Significant benefits have been observed in conditions such as Crohn's disease and ulcerative colitis. Hyperbaric therapy presents potential benefits for the infertility, improving the environment for blastocyst implantation and pregnancy.

CONCLUSION:

There is no doubt that HBOT has a beneficial impact on treatment of many systems such as the nervous, cardiovascular, digestive, and skeletal. This innovative approach of hyperbaric therapy extends to selected disorders such as neurodegenerative diseases, Crohn's disease, ulcerative colitis, and infertility.

Keywords: Hyperbaric oxygen therapy; inflammation; neuroprotection; Alzheimer disease; Parkinson disease; Crohn disease; ulcerative colitis; infertility

1. INTRODUCTION:

In 1662, Nathaniel Henshaw, a British physician, made significant advancements in the field by introducing hyperbaric therapy. His innovative technique involved placing patients inside a pressurized air chamber. Later in 1775 John Priestley's discovery laid the groundwork for the transition from compressed air therapy to inhalation of 100% oxygen under increased ambient pressure. However, in 1789 Lavoisier and Seguin discovered, that highly concentrated oxygen bears toxic effects on the human body. After many years, Paul Bert’s - "father of hyperbaric physiology" conducted to research on the adverse effects of hyperbaric oxygen on the central nervous system, particularly the manifestation of seizures. In 1937 Behnke and Shaw made another breakthrough by successfully utilizing hyperbaric oxygen therapy for the medical care

of decompression sickness. This accomplishment further underscored the therapeutic potential of hyperbaric oxygen and helped solidify its place in clinical practice. [1]

The physicochemical aspect:

The primary method of oxygen delivery to cells in the human body is through gas exchange, predominantly occurring in the respiratory system and to a lesser extent through the skin. This exchange in the lungs and cells relies on diffusion, where oxygen molecules migrate from areas of higher concentration to those of lower concentration. The rate of diffusion is influenced by the disparity in gas concentrations, referred to as partial pressure. The greater the difference in partial pressures of gases between two areas, the faster diffusion occurs. [2, 3]. The oxygen content in the air is 21% of the Earth's atmosphere, as per air composition. Oxygen diffuses across the alveolar-capillary barrier from the air-filled alveoli to the blood in the respiratory system. Similarly, oxygen permeates from the atmosphere into skin cells.

According to the above principle, the amount of dissolved gas correlates directly with its pressure.

Higher pressure allows for greater gas solubility in a liquid.

Clinical research indicates that under normal atmospheric pressure conditions, plasma typically holds about 3 ml of dissolved oxygen per 1 liter of blood when breathing air. However, when breathing pure oxygen this radio increases to 20 ml per 1 liter of blood. Furthermore, breathing 100% oxygen under elevated pressure conditions, ranging from 2.0 ATA to 2.5 ATA, boosts oxygen solubility up to 50 ml per 1 liter of blood. [4,5]

2. REVIEW METHODS: The article was complied by analyzing data from PubMed and Google Scholar regarding effects of hyperbaric therapy.

3. THE STATE OF KNOWLEDGE:

3.1 The primary effects of hyperbaric oxygen therapy: [6,7,8]

- Increased oxygen supply to the damaged area,
- Enhanced blood circulation in the affected region by constricting central vessels and escalating flow through injured tissues,
- Reduced swelling in damaged tissues,
- Inhibited bacterial proliferation and bolstered effectiveness of antibiotic therapy,
- Activated neoangiogenesis,
- Proliferated dermal cells and boosted collagen synthesis,
- Amplified antibacterial activity,
- Increased activity of osteoblasts and osteoclasts,
- Reduced half-life of carboxyhemoglobin,

- Reduced volume of gas bubbles in the bloodstream,
- Minimized adhesion of leukocytes in reperfusion insult,
- Prevented liberation of proteases and free radicals.

Healing properties of Hyperbaric Oxygen Therapy	
Nervous system	• stimulates nervous system function. • improves metabolism in nerve tissue. • decreases brain swelling. • improves microcirculation. • increases blood-brain barrier permeability. • reduces pain. • enhances sleep quality. • alleviates depressive states. • revives and energizes dormant cells. • restores proper cellular function (rehabilitation after stroke) [9]
Cardiovascular system	• promotes capillary formation, provides oxygen that nourishes and helps restore circulation in the areas obstructed by clots or diseased tissues. • increases the supply of oxygen to the heart, which effectively prevents damage to the myocardium and reducing the risk of heart attacks, particularly in individuals with coronary syndrome. • improves vascular elasticity and blood viscosity, leading to enhanced blood flow to all tissues and organs [10]

Healing properties of Hyperbaric Oxygen Therapy	
Digestive system	• boosts stem cells production, promoting cell regeneration and revitalization (in case of problems with food reflux, stomach ulcers), • eliminates inflammation in the body, • improves blood and lymphatic circulation, • supports nutrient absorption and cellular detoxification processes • enhances the performance of internal secretion organs, accelerates metabolism and increases the metabolic rate (supports weight loss) • supports treatment of many diseases, such as: bowel obstruction, enteritis, inflammatory bowel disease, pancreatitis, peptic ulcer disease, erosions and ulcers [11]
Skeletal system	• osteomyelitis • osteoporosis (increases bone mass by stimulating the production of osteoblasts) • osteonecrosis • osteoarthritis [12]
Recovery	• treatment of acute and chronic spine pain (sciatica, brachialgia, radiculopathy) • stimulates the growth of fibroblasts, collagen and elastin, therefore it is used for recovery after surgical and orthopedic procedures such as endoprosthesis, fractures, sprains, skin-grafts and burns [13] • regeneration after training (quick return to form after injuries, reducing muscle soreness) [14] • increases the body's efficiency and performance • reduces recovery time after physical exercise [15]

Healing properties of Hyperbaric Oxygen Therapy	
Inflammation	• decreases levels of tumor necrosis factor (TNF-alpha) and other inflammation markers like CRP (C-reactive protein), reduction of proinflammatory cytokines, including: IL-1β, IL-6, IL-18 [16] • control non-healing wounds, non-healing diabetic ulcers [17] • stimulates immune function, strengthening the body's natural defenses • detoxifies the body by eliminating toxins and heavy metals, including carcinogens. • enhances microcirculation in blood vessels and lymphatic channels. • augments the production of stem cells, facilitating cellular regeneration. • significantly relieves pain [18]

3.2 Innovative approach of hyperbaric therapy in selected disorders

3.2.1 Neuroprotective effects of hyperbaric oxygen therapy

Neurodegenerative disorders cause gradual damage to nerve cells and the subsequent loss of these cells, resulting in diminished motor or cognitive abilities. Conversely, oxidative stress and inflammatory responses are significant contributors to the development of such conditions. [19] HBOT effectively improves mitochondrial function in the spinal cord and motor cortex in motor neuron disease, leading to substantial delay in disease onset. Diseases linked to reduced oxygen supply predispose individuals to neurodegeneration, which highlights the significant role of hypoxia in neurodegenerative diseases (NDDs). Hypoxia-inducible factor-1 (HIF-1), a crucial transcriptional factor essential for cellular and tissue adaptation to low oxygen levels, has been associated in several NDDs, including Alzheimer’s (AD), Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS) and Parkinson’s (PD) making it a potential target for medical intervention. Hypoxia contributes to various pathological processes in NDDs, including: tau hyperphosphorylation, blood-brain barrier dysfunction, accumulation of β-amyloid (Aβ), neuronal degeneration. [20]

Alzheimer’s disease

Conditions associated with hypoxia, such as stroke and cerebral ischemia, greatly increase the incidence of AD. Early stages are characterized by cerebral hypoperfusion leading to hypoxia,

which correlates strongly with functional decline and structural changes in the brain. HBOT may mitigate neuroinflammation in Alzheimer's disease by reducing the levels of microgliosis, astrogliosis, TNF-α, and IL-1β, while increasing the expression of arginase 1, IL-10, Scavenger receptor A and IL-4. HBOT boosts in vitality, brain metabolic activity and cognitive function. [21, 22]

Parkinson’s disease

Brain injury caused by hypoxia worsens the expression and conglomerating of α-synuclein - pathological hallmark. There is a proposition that hypoxia, facilitated by HIF-1α in dopaminergic cells, increases the activity of ATP13A2 (PARK9), a transcription factor found with mutations in postmortem cases of PD. Studies on Parkinson's disease have indicated that exposure to mild HBOT for 11 weeks can prevent the loss of dopaminergic neurons induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. HBOT also positively affects aspects other than movement of such as severe depression and anxiety. [23]

Amyotrophic lateral sclerosis (ALS)

The detrimental effects on nerve cells and their subsequent death caused by oxygen deprivation entails a multifaceted interaction between various factors, such as disrupted mitochondrial function, oxidative stress, inflammation, imbalance in metal levels, apoptosis, synaptic dysfunction, and impaired autophagy, all collectively leading to the decrease in the number of neurons. Impaired microcirculation in the cerebromicrovasculature is another factor influencing the development of dementia and age-related cognitive decline. HBOT reduces tiredness and enhances muscular strength. [24]

3.2.2 Application of hyperbaric oxygen therapy in gastrology

Peptic ulcer disease

Research findings indicate that the combination of routine pharmacotherapy with magnetic field therapy, acupuncture and hyperbaric oxygen therapy yields the most favorable outcomes in patients. Specifically, hyperbaric oxygen therapy is highly recommended for older patients with peptic ulcers who also have coexisting conditions such as atherosclerosis and coronary artery disease. Utilizing combination therapy not only enhances therapeutic efficiency but also expedites the healing process of erosions and ulcers. Moreover, in patients receiving H2 blockers for duodenal ulcers, hyperbaric therapy has been observed to increase the concentration of prostaglandin PGE in gastric juice. Prostaglandin plays a crucial role in regulating microcirculation and stimulating bicarbonate production. When employed as an adjunctive therapy for perforated gastric and duodenal ulcers, hyperbaric therapy reduces post-operative rehabilitation time by half and diminishes lowers post-surgical complications by more

than 50%. In patients experiencing hemodynamic and respiratory disorders due to upper gastrointestinal bleeding, a complication of peptic ulcer disease, improved hemodynamic stability of the circulatory system is observed, eliminating the need for assisted breathing support.

Intestinal obstruction

There is a notable decrease in the volume of intestinal gases, a reduction in the diameter of obstructed intestinal loops, and an improvement in intestinal contractility, leading to normal peristalsis. Additionally, oxygenation of the intestinal wall enhances tissue survival in the affected obstruction area and boosts proper motility. This process also facilitates the return of the diaphragm to its normal position, thereby restoring adequate ventilation and promoting improved venous return. The application of hyperbaric oxygen enhances the antibacterial functions of leukocytes, resulting in the inhibition of bacterial multiplication and a notable decrease in the production of endotoxins by bacteria. In cases of intestinal obstruction consequent on to conditions like Hirschsprung's disease or developmental defects of the anus and rectum, providing hyperbaric therapy alongside surgical interventions shortens the duration of parenteral nutrition, significantly decreases septic complications, and improves blood supply to the intestinal walls. Additionally, it reduces intragastric reflux and minimizes the occurrence of anaerobic bacterial infections. [25]

Other afflictions

In cases of Hepatitis B, hyperbaric therapy demonstrates high effectiveness by reducing the activity of alanine aminotransferase and gamma-glutamyltranspeptidase, along with decreasing concentrations of IgG and IgM. Additionally, it diminishes the values of markers indicating inflammatory activity within the liver. Liver transplant recipients often benefit from hyperbaric oxygen therapy, as it significantly decreases the risk of thrombosis in the vessels of the transplanted liver, lowers the incidence of septic complications, and reduces the need for retransplantations. Moreover, administering hyperbaric oxygen following partial resection of the liver parenchyma helps normalize the concentration of glutamine in the serum, indicating the recovery liver function post-surgery. In cases of peripancreatic abscess, hyperbaric oxygen therapy offers relief from pain, normalization of body temperature, and reduction size of the abscess.

Inflammatory bowel disease comprises a group of chronic conditions that repeatedly affect the digestive tract, such as ulcerative colitis and Crohn's disease. HBOT could potentially alleviate

inflammation by boosting the antioxidant system, aiding the differentiation of colonic stem cells, and involving repair cells. [26]

Crohn's disease (CD) variety of inflammatory bowel disease (IBD), characterized by inflammation that extends through the entire thickness of the intestinal wall, commonly affecting the end of the ileum. The exact cause of this condition remains unknown, although research suggests it arises from a complex interplay between genetic predisposition, immune dysfunction and environmental factors. Patients with CD often exhibit a wide range of clinical symptoms, including abdominal pain, diarrhea, intestinal blockage, as well as systemic symptoms such as fever and malnutrition. As there is currently no definitive cure for CD, the primary goal of treatment is to induce and sustain periods of remission by managing inflammation. [27]

Several investigations have demonstrated the advantages of hyperbaric oxygen therapy (HBOT), particularly in managing challenging perineal wounds, pyoderma gangrenosum (PG), and fistulizing disease. The positive outcomes associated with HBOT are linked to both local mechanisms, such as enhanced neovascularization, reduced hypoxia, differentiation of stem cells, and formation of extracellular matrix, as well as systemic effects, including the reduction of proinflammatory cytokines and oxidative stress biomarkers. The pain relief, reduction in systemic corticosteroid usage, and accelerated healing observed in patients with pyoderma gangrenosum may be attributed to similar underlying mechanisms.

Regarding the use of hyperbaric oxygen therapy (HBOT) in enterocutaneous fistulas, it may be suitable when the output volume is low. However, in cases of complicated fistulas with higher output, a chronic course, labiated appearance and distal obstruction, initial conservative management may be attempted, although surgery typically remains the definitive treatment. [28]

Ulcerative colitis (UC) is a chronic condition characterized by periods of regress and remissions, often resulting in ulcers in the colon and rectum. The reason remains unknown, with current research pointing towards aberrant immune responses within the intestinal environment of genetically predisposed individuals. [29] Most patients have a benign or moderate symptoms of the illness, but one-fifth of them will be hospitalized at least once in their lifetime. Treatment depending on the stage of UC, to begin with 5-aminosalicylic acid drugs for mild to moderate cases to steroids for severe acute episodes. For patients who don’t respond to steroids, treatment like cyclosporine or methotrexate may be examined. Additionally surgical treatment is associated by numerous harmful effects, both physical and psychological.

Therefore, clinicians are eager to uncover new therapeutic approaches that effectively address severe UC with undesirable effects. [30]

In available sources the following cases have been described:

- For 8 years, Crohn's disease resisted both surgical and medical interventions, including corticosteroids, sulfasalazine, metronidazole, and 6-mercaptopurine. However, within just 2.5 months of receiving HBOT, there was complete and remarkable healing. The patient required further HBOT sessions over the course of 11 months, which resulted in sustained improvements.
- The patient had Crohn's disease that was unresponsive to standard treatments, including prednisolone, sulfasalazine, and an elemental diet. After undergoing HBOT, an endoscopic examination confirmed complete healing of a rectal ulcer. At the time of the study's publication, the patient had maintained clinical remission for 7 months.
- 10 individuals diagnosed with Crohn’s disease, unresponsive to conventional medical therapies, participated in the study. Out of these, 8 patients exhibited improvement, and notably, 6 achieved complete healing.
- A patient with severe, treatment-resistant Crohn’s disease, having previously unresponsible to sulfasalazine and corticosteroids, experienced complete recovery following hyperbaric oxygen therapy (HBOT). Throughout the 24-month follow-up period post-HBOT no disease recurrence have been observed.
- Ulcerative colitis resistant to standard medical treatments (such as corticosteroids for 22 months, 6-mercaptopurine, mesalamine, and tetracycline); notable enhancements and clinical remission achieved through HBOT (lasting for 2 months).
- In patients with ulcerative colitis showed resistance to standard medical therapies (mesalamine and prednisolone) progression were noted within a few weeks, symptoms relief, including cessation of bloody diarrhea.
- All patients suffering from chronic ulcerohemorrhagic colitis improved after first 5-6 treatments. [31]

3.3.3 Infertility

Infertility is indeed a significant issue globally, affecting approximately one in six couples from diverse backgrounds and regions. Among the myriad factors contributing to female infertility, the quality of the endometrial lining stands out as a critical determinant of successful embryo implantation. Endometrial receptivity, referring to the readiness of the uterine mucosa to accept and nurture an embryo, is essential for achieving pregnancy. Various factors, such as hormonal imbalances, uterine abnormalities, and certain medical conditions, can compromise this. [32]

In recent years, remarkable progress in reproductive medicine has ushered in a range of assisted reproductive technologies (ART) designed to tackle infertility head-on. Among these, in vitro fertilization (IVF) and intrauterine insemination (IUI) have emerged as prominent options, offering hope to couples grappling with fertility challenges. Moreover, ongoing research endeavors are dedicated to exploring innovative treatments and strategies aimed at enhancing endometrial receptivity. By delving deeper into the complexities of the uterine lining and its role in embryo implantation, scientists aim to bolster the chances of successful pregnancy for couples navigating the difficult journey of infertility. [33]

Understanding the physiological mechanisms behind hyperbaric therapy and its impact on various tissues, particularly in oxygen-deprived conditions, suggests potential benefits for tissues undergoing rapid cell proliferation, such as the endometrium. Its foundation lies in the regular anatomy of the uterus and its cavity, alongside optimal hormonal balance, vascularization, and oxygenation.

This surplus oxygen supply can enhance cellular function and metabolism, which may be particularly advantageous for tissues experiencing hypoxia.

In the context of the endometrium, which undergoes cyclic regeneration and thickening in preparation for embryo implantation during each menstrual cycle, hyperbaric therapy may offer advantages. [34] By providing an abundance of oxygen to the endometrial tissue, hyperbaric conditions could promote optimal development and thickening of the endometrium, creating a more conducive environment for blastocyst implantation and subsequent pregnancy.

While further research is necessary to fully understand the specific effects of hyperbaric therapy on endometrial health and fertility outcomes, the potential for enhanced oxygen delivery to promote endometrial development offers hope for couples facing infertility challenges. [35]

4. CONCLUSION

Hyperbaric therapy utilizes high pressure oxygen response. It elevates the concentration of oxygen in hemoglobin and plasma. Based on its solubility, when pressure increases so does the diffusion gradient for its delivery deeper into tissues, which is the main mechanism. HBOT serves as both a primary and alternative treatment for infections, especially in cases of antibiotic-resistant pathogens. It aids in infection healing through direct bacteriostatic or bactericidal effects, boosts immune system antimicrobial activity, and synergizes with antimicrobial agents. When safety protocols are adhered to, HBOT proves to be an effective procedure with minimal side effects. There is no doubt that HBOT has a beneficial impact on treatment in many systems such as the nervous, cardiovascular, digestive, and skeletal. This innovative approach of hyperbaric therapy extends to selected disorders such as

neurodegenerative diseases, Crohn's disease, ulcerative colitis, and infertility. Additionally, it has a wide range of applications in disease prevention and body regeneration.

Disclosures

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