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Pleiotropic Effects of Hyperbaric Oxygen Therapy and Its Potency as Supplemental Therapy

Manoj Gupta*[1], Bhakti Gupta[2]
[1] Hyperbaric Physician, Head of Department of Hyperbaric Medicine, Kiran Hospital and Medical College, Surat, India
[2] MSc Nutrition,PGDHA, LLB(g), Director Prana Hyperbaric oxygen Centre, Mumbai.

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*Corresponding Author:

Manoj Gupta
Hyperbaric Physician, Head of Department of Hyperbaric Medicine, Kiran Hospital and Medical College, Surat, India

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) is a therapeutic technique of administering oxygen at high purity under pressure higher than the normal atmospheric pressure. Oxygen has an inherent capacity to stimulate physiological and biochemical changes which have a great therapeutic value. The effects include enhanced bactericidal activity by enhancement of immune cells, reduction of edema by promoting vasoconstriction, maintenance of an oxidative environment which promotes vascularization, collagen synthesis, and localized free radical production. Due to a wide array of its functional attributes, HBOT finds use in a large number of clinical indications as an adjuvant therapy especially in post-clinical and recovering patients. HBOT has proved to be beneficial in clinical applications but requires a thorough understanding of the underlying mechanism of therapeutic action to establish it as a standard therapeutic approach. This review gives an account of the development of HBOT from a historical perspective and its current applications, efficacy, and future prospects as a therapeutic intervention.

Keywords: Hyperbaric, Wound Healing, Hyperbaric Chamber, Normobaric, Hyperoxia, Regeneration.

INTRODUCTION:

The human body is sensitive to changes in atmospheric pressure, which has been shown to have a variety of health consequences[1-4]. 'Sea level' pressure refers to the surrounding atmospheric pressure to which we are exposed. The pressure imposed by the atmosphere above us lessens as we ascend in altitude. Nathaniel Henshaw, a British physician and clergyman, claimed the first medicinal use of increased pressure[5, 6]. However, he did not offer any scientific explanationfor this [6, 7].

HBOT is a technique in which the patient is kept in an enclosed chamber with 100% oxygen at a pressure greater than 1 atmosphere absolute (ATA) or 760 millimeters of mercury[8]. Intermittent hyperbaric hyperoxia is created by maintaining the patient under such high pressure, and it has been linked to improved wound healing, angiogenesis, and other physiological changes[9, 10]. The partial pressure of gases in the surrounding atmosphere affects living creatures, which is proportional to their percentage in the atmosphere. Changes in gas partial pressure have a direct impact on cells, tissues, and organs because the applied force of these gases increases or decreases, affecting the density of gases in gas-filled bodily cavities such as the lungs as well as their partial pressure in the blood[11, 12]. At a cellular level, a body exposed to high atmospheric pressure experiences alterations in membrane composition and cytoskeletal architecture[13, 14]. As a result, changing an individual's surrounding pressure may cause changes in cellular activities. Also, the hyperbaric effect of different atmospheric gases varies due to their differential atmospheric and physiological concentrations. In natural conditions, a change in atmospheric pressure is experienced with the change in the altitude. People who live at higher altitudes, for example, are subjected to lesser pressure than those who live at sea level. Deep sea divers, likewise, feel more pressure as they dive deeper due to the pressure exerted by the water above them. Thus, the application of hyperbaric oxygen for therapeutic purpose requires knowledge of behavior of gases and its functions with respect to human physiology. At higher oxygen partial pressure, the fraction of dissolved oxygen in plasma also increases[15, 16]. Therefore, it is essential to carefully design the modalities of therapeutics as per the presented conditions. The therapeutic effects generated during the course of HBOT depend primarily on the increased partial pressure of oxygen but the outcomes are not limited to it. To show its restorative effects, HBOT also works on a biochemical and physiological level. However, research on its indirect effects is sparse, and the underlying processes of its role on a biochemical and cellular level must be investigated further.

Air contains roughly 20% oxygen, 79% nitrogen, and 1% carbon dioxide, as well as several trace gases, at normal temperature and pressure. The partial pressure of oxygen in arterial blood equates to 75-100 mm Hg under these conditions[17]. The level of arterial blood oxygen, and consequently the partial pressure of oxygen, can rise much above 100 mm Hg under hyperbaric conditions.

The oxygen content of blood or plasma can be derived by using Henry's Law[18, 19] as:
O_2 content of blood (Vol %) = (0.0031 × pO_2) + (Hb conc. × 1.36 × SaO_2)

The determination of blood oxygen concentration under hyperbaric settings allows for effective HBOT therapy design. During therapy, it's also vital to consider the impact of pressure on physiological activities. The human body is extremely sensitive to variations in pressure and responds by constricting blood vessels, slowing heart rate, and releasing RBCs stored in the spleen[2]. The lungs are the central respiratory organs that provide oxygen to all cells and tissues in the body. As the alveolar and arterial oxygen pressures rise sharply under hyperbaric settings, an increase in pO_2 causes hyperoxic conditions. When compared to the lungs, it has been discovered that cells and tissues attain pO_2 equilibration at a slower rate[17, 20, 21]. When the pO_2 reaches equilibrium at a pressure of 2 ATA, it can reach as high as 300 mm Hg. Vasoconstriction occurs in systemic arteries in response to high arterial pO_2, lowering arterial input. This causes tissue fluid resorption, which prevents edema. Tissue healing is linked to oxygen-dependent activities including fibroblast proliferation and collagen formation[22]. The rate of fibroblast proliferation and collagen production increases when pO_2 rises, resulting in quicker wound healing. Furthermore, due to increased fibroblast activity and collagen synthesis, the creation of a vascular network is accelerated[23, 24]. Oxidative stress is produced as a result of elevated pO_2, allowing immune cells to commence intracellular death via oxidative free radicals[25, 26]. This reduces the infectious state of tissues, but it also increases the risk of oxidative damage to cells and tissues.

We have presented a brief outline of HBOT's developmental history, mechanism of action, and concepts supporting its use in the treatment of numerous illnesses in this article. HBOT has been shown to have a positive effect in a variety of clinical problems owing to its pleiotropic effect in growth, maintenance and modulation of microenvironment (**Fig. 1**). However, the treatment strategy needs to be carefully designed to minimize the side effects associated with the technique. We have also discussed the current status of HBOT as a therapeutic technique against a myriad of clinical conditions and the future prospects of its development and better utilization.

2. Role of oxygen in cellular regeneration and wound healing

Wound healing is a complicated process that necessitates the interaction of a range of cells in the microenvironment of healing wound. Following the creation of a fibrin clot, wound healing entails the establishment of hemostasis in the wound site. Clot formation is succeeded by the infiltration of immune cells and inflammatory cells such as monocytes, neutrophils and dendritic cells which functions to check any infection and clear cellular debris. Once the inflammatory stage is over, cellular regeneration and angiogenesis occurs to initiate wound healing and vascularization. In the later stages of healing, fibroblasts play an important role in the formation of contractile granulation tissue for wound closure and deposition of extracellular matrix[27-29]. In some circumstances, the wound healing process necessitates medical intervention in order to improve the wound healing process. This is particularly important in surgical wounds, trauma cases, severe burns, and individuals with clinical disorders that impair wound healing, such as diabetes and sickle cell anaemia[30-33].

Both in the inflammatory and regenerative phases of wound healing, oxygen plays a critical function in the microenvironment. Tissue hypoxia has been linked to a higher risk of wound infection and a longer time for wound healing. Supplementing oxygen throughout the wound healing process, on the other hand, reduces the danger of infection and speeds up the healing process. For the generation of reactive oxygen species(ROS), immune cells and inflammatory cells such as neutrophils require oxygen as a substrate [34]. Furthermore, oxygen is necessary for the production of granulation tissue and serves as a cofactor in collagen synthesis by mediating proline hydroxylation[35, 36].

Neutrophils mediate the formation of ROS during the inflammatory stage of wound healing to resist bacterial infection. Under these conditions, neutrophils' oxygen consumption increases, resulting in a respiratory burst. Allen *et al.,* in his *in vitro* investigation discovered that oxygen consumption by neutrophil is directly proportional to available oxygen[37]. This shows that a higher oxygen concentration encourages neutrophils to produce more ROS, which boosts antibacterial activity. Greif *et al.* conducted an *in vivo* study on the role of oxygen in wound infection prevention by providing either 30 percent or 80 percent oxygen to a group of 500 patients intra-operatively or two hours after surgery[38]. The numbers of surgical site infections (SSIs) were much lower in the 80 percent oxygen supplementation group. In a comparable study by Belda *et al.,* the rate of SSIs was lowered by about 10% in the 80 percent oxygen supplementation group (14.9 percent SSIs) compared to the 30 percent oxygen supplementation group (24.4 percent SSIs)[39].The percentage of inspired oxygen (FiO_2) and time duration, on the other hand, are important factors in the effectiveness of oxygen supplementation. Based on what is known about the role of oxygen supplementation in wound healing, it is clear that a larger proportion of FiO_2sustained for a short length of time is not harmful to healthy tissues and the respiratory system.

For the promotion of enhanced wound healing, the use of oxygen in facilitated wound healing under high pressure has been used. For cells involved in immunological response, inflammatory response, tissue regeneration, and vascularization, a hyperbaric environment causes an increase in cellular activity. It has been demonstrated that tissues become sensitized to greater levels of ROS in a hyperbaric oxygen environment, limiting the extent of oxidative damage to healthy tissues.

Angiogenesis, the production of new blood vessels to vascularize newly created tissues, is another part of wound healing that is dependent on the presence of oxygen.Hypoxic circumstances are thought to increase angiogenesis by activating hypoxia induced factor-1 (HIF-1) and vascular endothelial growth factor (VEGF)[40]. However, several research, on the other hand, show that this is not the case. Studies on a mouse model of neovascularization revealed that hyperoxic conditions promote angiogenesis while hypoxic conditions inhibit it[41]. Similarly, Sander *et al.* found that when mice are exposed to hyperbaric oxygen, the rate of neovascularization increases considerably[42]. Collagen synthesis is an important step in the wound healing process because it creates the extracellular matrix (ECM), which helps to reinforce scar tissue and provides a place for fibroblasts to deposit[43, 44]. Collagen creation is dramatically reduced in hypoxic conditions during wound healing[44]. Oxygen supplementation, on the other hand, is effective in promoting collagen synthesis and deposition. HBOT was found to promote fibroblast infiltration and collagen deposition in porous polyethylene implants in the skin in a rat wound healing model[43]. The influence of oxygen on collagen production in humans has only been studied in a few cases. The combined effect of HBOT and basic fibroblast growth factor (bFGF) on collagen synthesis was proven by Nakada *et al.,* however there is no evidence for the solitary effect of oxygen[45]. The overall effect of HBOT on cell migration, cell proliferation, ECM deposition and oxidative environment leads to improved wound healing and revascularization (**Fig. 2**).

3. Pressure effects on human physiology

Through homeostasis, the human body maintains a constant level of physiological activities and circumstances. The body perceives changes in the surrounding environmental factors, such as temperature, humidity, and pressure, as a stimulus and responds appropriately to maintain homeostasis[46, 47]. Similarly, when the human body is exposed to fluctuations in air pressure, physiological and cellular changes occur. The volume of gases stored in organs having gas-filled cavities fluctuates as the pressure applied to the body increases or lowers. Changes in partial pressure of gases have an impact on cytoskeletal arrangement and lipid bilayer membrane organization at the cellular level[13-15]. For a long time, extreme changes in atmospheric pressure can have negative physiological and neurological consequences.

The pressure above the sea level corresponds to 1 ATA which is defined as normobaric pressure. As altitude increases, the air density as well as atmospheric pressure decreases. The decrease in partial pressure of oxygen at higher altitudes creates hypobaric conditions, which has acute physiological implications[48, 49]. The alveolar partial pressure of oxygen gets reduced drastically at reaching higher altitudes and can even become zero at around 15000 m altitude[50]. Thus, supplemental oxygen is required upon progression into higher altitudes. Increased hyperventilation occurs as a salvage mechanism to absorb maximum oxygen into lungs. At the same time, this also leads to decreased partial pressure of carbon dioxide. Other physiological changes under hypobaric conditions include increased heart rate and decreased cognitive abilities[20, 48].

Individuals in natural conditions during deep sea diving endure pressures greater than the typical air pressure due to the weight of water columns above the diver. There is a rise of 1 ATA for every 10 meters below sea level. Similar to hypobaric conditions, higher atmospheric pressure also causes physiological and cellular effects. Hyperoxia, hypoventilation to adjust for higher partial pressure of oxygen, slowed heart rate, and increased diuresis are the key physiological changes associated with hyperbaric circumstances[51]. The alveolar pO_2 is 100 mm Hg, but at 3 ATA, it can rise to 2280 mm Hg. The oxygen concentration of blood rises to 23 ml O_2/dL at this pressure, up from 16.2 ml O_2/dL at normal pressure[52-54]. Under hyperbaric conditions, the hyperoxic state causes vasoconstriction, which reduces blood flow. Despite the lower blood flow, the oxygen delivery to tissues is increased due to the greater pO_2[55]. The therapeutic impact of elevated oxygen levels in the blood can be attributed to HBOT, although the processes by which these effects are exerted are less well understood.There is a huge variability in the treatment protocols of HBOT for various ailments but still there are some general considerations in recommended treatment strategies (**Table 1**).

4. Historical Account Of HBOT

For millennia, the influence of pressure on the functioning of the human body has piqued interest, leading to the creation of equipment and ways to harness the phenomena for therapeutic purposes. Earlier works carried out in the field of HBOT demonstrated promising outcomes and laid the foundations for modern techniques in HBOT **(Fig. 3)**.In 1662, Nathaniel Henshaw, a British priest and physician, first utilized the hyperbaric conditions for therapeutic purposes[56]. In order to generate a hyperbaric (pressure higher than normal atmospheric pressure) or hypobaric (pressure lower than normal atmospheric pressure) atmosphere, he created an enclosed room known as a 'domicillium', which utilized organ bellows and valves to regulate the air pressure of a sealed chamber. Henshaw utilized the 'domicillium' for the treatment of stomach and respiratory disorders. The overall goal was to use pressure fluctuations to treat chronic illnesses mostly affecting the respiratory and digestive systems. He did not, however, give any scientific support for his technique's

therapeutic effects. Henshaw's design had a number of significant flaws, including the retention of metabolic waste gases due to an unventilated system, achieving a modest variation in pressure, and limitations in the desired therapeutic effect due to the compression of ambient atmospheric gases rather than purified oxygen during the procedure [57].

John Priestly discovered oxygen in 1775, and his discovery had a significant impact on the development of hyperbaric treatment[57]. A hyperbaric chamber was invented in 1834 by a French physician named Junod, based on a design by James Watt, the man who is credited with inventing the steam engine. Junod's hyperbaric chamber could achieve a relatively greater air pressure in the region of 2 -4 atm. He dubbed the method "Le baind'aircomprime" after the apparatus he used to treat pulmonary problems (the compressed air bath). The therapeutic implications of the compressed air bath, according to Junod, derive from improved oxygen circulation to the internal organs, including the brain, resulting in a sensation of well-being in the treated patients[6].

Several variations and improvements in the design of hyperbaric chambers were introduced in later years by various workers. Emile Tabarie, a French physician, designed a spherical pneumatic chamber in 1832 and provided a thorough explanation of his work to the French Academy of Sciences. His research established the necessity of pressure fluctuations during therapy and formed the groundwork for modern HBOT[56]. Jacques Triger was a French palaeontologist and mining engineer who developed compressed metal caissons that were lowered into the mines and pressurized using air compressors on the surface. Triger's caisson allowed mine workers to work for long periods of time at a depth. When the personnel returned to surface pressure, they complained of joint discomfort and CNS abnormalities. This was first referred to as caisson's disease, but after more research, it was identified as decompression sickness[6, 56]. Pravaz built a hyperbaric chamber in 1837 that could hold 12 patients at a time and utilized it to cure a variety of disorders including pulmonary diseases, deafness, cholera, conjunctivitis, and rickets[6, 56]. In 1921, an American physician named Orval J Cunningham created a hyperbaric chamber for the treatment of patients suffering from Spanish influenza during the last days of World War I. During the course of treatment, he saw a considerable improvement in the patients' situations. In addition, he built the world's largest hyperbaric chamber in Cleveland, Ohio, in 1928, with a five-story edifice with 12 rooms dedicated to hyperbaric therapy on each floor. Despite the fact that his work became well-known, he was unable to have his conclusions validated by the American Medical Association (AMA). HBOT was first developed as a secondary treatment for a small number of disorders. Due to the scientific justification created over time, it has gained legitimacy as well as appeal among physicians and patients as an effective treatment technique [58, 59].

5. HBOT chambers

Hyperbaric chambers are specialized chambers that sustain a pressure higher than atmospheric pressure. The settings within a hyperbaric chamber are tightly controlled and can be adjusted to meet the needs of the patient receiving treatment. They are classed as monoplace or multiplace hyperbaric chambers based on the capacity of the chamber[60]. Monoplace chambers are meant to keep a single patient at a pressure of up to 3 ATA. Oxygen can be supplied to the chamber through continuous purging with an input and outlet, or it can be recycled once the undesired gases have been removed. The monoplace chamber's design is appropriate for patients who require acute care and can be watched from the outside. External intervention is kept to a minimum during treatment to ensure adequate isolation and infection prevention[61, 62]. Multiplace hyperbaric chambers are larger and can accommodate a larger group of patients. It has the capacity to treat up to 20 patients at the same time. The oxygen is delivered by gas masks that cover the mouth and nose. Throughout the treatment time, temperature and humidity are regularly monitored and maintained. In addition, for the treatment of patients with decompression sickness, the operating pressure can be increased to a higher value of up to 6 ATA[61, 62]. Furthermore, monoplace chambers have a higher risk of fire due to the presence of oxygen at high pressure throughout the chamber, whereas multiplace chambers have a lower risk due to the usage of masks.

Hyperbaric chambers are also classified as soft or hard hyperbaric chambers based on their composition [61]. Soft hyperbaric chambers are made of a soft polymeric material like polypropylene and can be sealed with a zipper. Up to 1.3 ATA and 24 percent O_2, the ambient pressure and oxygen levels can only be moderately increased. These are primarily suited for mountain climbers and divers. Hard hyperbaric chambers are hard-shelled chambers that can achieve higher atmospheric pressures and 100% oxygen levels. These are therapeutic hyperbaric chambers that have been approved for the treatment of 14 distinct clinical disorders[8]. Installation of hyperbaric chambers involves rigorous safety procedures due to a significant potential of fire hazard.

6. Applications of HBOT

6.1 Gas or air embolism

A gas embolism, also known as an air embolism, is a medical disorder in which gas bubbles form in the arterial or venous circulation[63]. Gas embolism is divided into two types based on the location of gas bubble entrapment: arterial gas embolism (AGE) and venous gas embolism (VGE). It is caused by abrupt changes in an individual's surrounding air pressure. During their ascent from the water, divers, for example, suffer from pulmonary barotrauma and gas embolism. Divers with lung conditions like as asthma or bullous illness are more susceptible to arterial gas embolism [64]. In some situations, an arterial gas embolism can be accompanied by neurological issues[64, 65]. During compressed gas diving, a venous gas embolism can occur without causing any clinical signs. If a substantial amount of gas is trapped in the venous

circulation, it can induce dyspnea, cough, and pulmonary edema [66]. SCUBA diving, as well as a variety of medical or surgical procedures such as lung needle biopsy, hemodialysis, and arthroscopy, can result in a gas embolism [67-70]. As soon as the clinical symptoms of a gas embolism occur, HBOT is suggested.

At high pressure, oxygen supplementation helps to maintain arterial oxygen content while also increasing the pace of bubble resorption. HBOT is typically not indicated for asymptomatic venous gas embolism therapy. The treatment of gas embolism with HBOT is advised at 100 percent O_2 at 2.82 ATA; however the settings can be changed depending on the clinical symptoms[71]. Throughout the surgery, airway management and blood pressure must be constantly monitored. As a result, multiplace chambers are thought to be better for HBOT therapy of gas embolism.

6.2 Carbon Monoxide Poisoning

CO inhalation is extremely poisonous, and sustained exposure to high levels of CO can be fatal. Nausea, vomiting, chest pain, disorientation, and exhaustion are some of the symptoms of CO poisoning[72]. The affinity of CO for haemoglobin (Hb) is 200 times stronger than that of oxygen[73, 74]. As a result, when CO poisoning occurs, CO preferentially binds to Hb, causing cellular respiration to be disrupted. CO poisoning patients may experience neurological symptoms as a result of inflammatory pathways being activated and oxidative stress caused by hypoxia.

Patients with more than 25% carboxyhemoglobin in their blood should have HBOT. When oxygen is supplemented during HBOT, the rate of CO dissociation from Hb increases, resulting in faster oxygenation [75, 76]. A single HBOT treatment is usually enough to cure the consequences of CO poisoning. The following two procedures for treating CO poisoning with HBOT have been proposed based on randomized clinical trials:

1. The initial compression level is kept at 3 ATA, then lowered to 2 ATA and held for 140 minutes. Then, at six to twelve hour intervals, two HBOT sessions at 2 ATA for 90 minutes (with five minutes of normobaric air breathing breaks to mitigate O_2 toxicity) are performed.
2. Initial compression to 2.8 ATA, then lowered to 2 ATA and maintained for 120 minutes without any more hyperbaric oxygen.

HBOT has therapeutic effects because it causes quick CO removal from the blood while also oxygenating it. HBOT reverses several clinical signs of CO poisoning, including cellular respiration inhibition, enhanced inflammatory response, tissue necrosis, and apoptosis.

6.3 Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) is a disorder in which the arteries providing blood to the retina become blocked, resulting in sudden visual loss in one eye[77, 78]. The blockage may occur in the central retinal artery or cilioretinal arteries due to blood clot or cholesterol. Patients who have high blood pressure, diabetes, or glaucoma are more likely to get CRAO[79-81]. Multiple branches of the central retinal artery supply blood to the inner layers of the retina. There are around 20 short posterior ciliary arteries and two long posterior ciliary arteries in the human body [79]. The extra ocular muscles are supplied with blood via the anterior ciliary arteries, which branch off from the ophthalmic artery. Retinal blood circulation is restricted when the central retinal artery or the ciliary arteries are blocked, resulting in visual loss[82]. HBOT has been discovered to be helpful in the treatment of CRAO since the retina is one of the most oxygenated organs in the human body. When considering HBOT as a therapy option for CRAO, there are a number of considerations that need to be taken into account. Patients' degrees of occlusion may differ, and their responses to treatment may differ as well. If the retinal tissue is irreversibly injured, restoring blood flow to the retina will not result in vision restoration. Furthermore, if the ophthalmic artery and the posterior ciliary arteries are both closed, oxygenation of the inner layers of the retina is impossible. To keep the retina alive until blood circulation is reestablished through recanalization, an acceptable partial pressure of oxygen must be maintained [83]. As a result, it's critical to start treatment as soon as possible to restore eyesight before ocular tissue damage develops. The removal of blockage is usually accomplished through the administration of thrombolytic drugs and surgical removal of thrombus [84]. When there is no tissue necrosis and retinal circulation may be restored with recanalization, HBOT is recommended as a therapy option. Under hyperbaric conditions, oxygen supplementation is not always required to reverse retinal ischemia. A mixture of O_2 (95%) and CO_2 (5%), in most cases, is recommended for treatment[85-87]. The partial pressure of O_2 rises during treatment, causing vasoconstriction of the retinal arteries. CO_2 helps in countering the effect of vasoconstriction.

6.4 Idiopathic Sudden Sensorineural Hearing Loss

Idiopathic sudden sensorineural hearing loss (SSNHL) is defined as a loss of 30 decibels or more in less than 72 hours[88]. The actual cause of the clinical ailment has yet to be determined. SSNHL has been associated with a number of pathophysiological conditions. SSNHL can be caused by ear infections, trauma, autoimmune illnesses, neoplasms, metabolic dysfunctions, vascular abnormalities, or neurological disorders, to name a few etiological reasons [89]. HBOT is helpful in the treatment of SSNHL because oxygen tension affects cochlear function and striaevascularis metabolism in the ear. Perilymphatic O_2 tension has been found to be considerably lower in patients with deafness who develop edema.

Supplemental oxygen can help restore intracochlear functioning and keep cochlear metabolism in check. HBOT causes vasoconstriction, which helps to reduce edema and maintain normal blood flow to the inner ear. As a result, neurosensory cells are protected and hearing is gradually restored[90]. The suggested HBOT protocol entails administering 100% O_2 at 2-2.5 ATA for 90 minutes per day, for 10-20 treatment sessions[90, 91]. After each therapy session, an audiometry test is repeated to track the improvement in hearing.

6.5 Wound Healing

Wound healing after an injury consists of several phases that are interrelated. Hemostasis, inflammation, proliferation, and remodeling are the four steps that make up the wound healing process. Each phase involves a complex interplay of biochemical pathways, signal transduction, immune cells, chemokines and cytokines [27]. Platelet aggregation, degranulation, and the production of numerous chemo-attractants and growth factors such as platelet derived growth factor, transforming growth factor-β (TGF-β), epidermal growth factor, histamine, and bradykinin are among the first processes in wound healing [27, 92]. The infiltration of immunological and inflammatory cells, such as polymorphonuclear leucocytes and macrophages follows after release of chemo-attractants. Lactate and proteases are produced by activated neutrophils and macrophages, resulting in an acidic environment and the breakdown of damaged extracellular matrix, respectively. The inflammatory phase also includes the respiratory burst, in which oxygen consumption can increase by up to 50 times its typical level [93]. As a result, a hypoxic environment is formed, which serves as a stimulant for optimal inflammatory and immunological responses. HBOT wound treatment is primarily based on the hyperoxygenation of the wound site, which aids in the maintenance of a greater oxygen partial pressure in the healing tissues.. Maintaining a high pO_2 in the healing tissues is the driving force behind HBOT wound healing, and the rate of repair is determined by pO_2 levels.

HBOT is used to improve wound healing in a variety of traumas and tissue necrosis situations. HBOT has been used to treat non-healing wounds, such as diabetic foot ulcers, which do not heal in a timely manner. In such circumstances, impaired wound healing is caused by hypoxic conditions in the wound microenvironment, as well as poor self-healing characteristics due to clinical factors[30, 94, 95]. HBOT creates a hyperoxic environment, which increases angiogenesis and fibroblast proliferation by stimulating the release of growth factors[96]. HBOT is also used to treat infections of the soft tissues, such as Clostridial myonecrosis and gas gangrene[97]. During the HBOT technique, hyperoxygenation suppresses the generation of bacterial toxins and enhances the formation of free radicals, as well as immune cell activation, all of which contribute in the battle against infection. HBOT has been found to be effective in the event of traumatic crush injuries and has been recommended depending on the severity of the damage[98, 99]. HBOT aids in the reduction of reperfusion damage, edema, and infection risk. The stabilization of wounds and the revascularization of injured tissues are aided by a hyperoxic environment. In the presence of poor circulation, skin grafts and flaps fail to mend and stabilize. In such circumstances, HBOT is recommended to boost oxygen availability to the healing wound in order to stimulate angiogenesis and vascularization, which would improve graft life[100]. Hypoxic conditions and altered tissue architecture in terms of tissue vascularization and attachment are linked to radiation-induced wounds and thermal burns[101, 102]. HBOT is effective in boosting angiogenesis and increasing capillary density, hence accelerating the wound healing process. Radiation and burn injuries cause fluid loss and edema. Vasoconstriction around damaged tissues helps to reduce fluid loss and edema. HBOT is particularly helpful in cases of burns caused by smoke inhalation or carbon monoxide poisoning.

6.6 Refractory Osteomyelitis

Refractory osteomyelitis is a type of persistent bone or bone marrow infection that returns after a course of treatment. Patients with predisposed medical conditions such as diabetes mellitus and peripheral vascular disease are more likely to develop bone infection. Even with long-term medication and surgical intervention, the recurrence rate is substantial in the majority of patients. The most prevalent infection that causes osteomyelitis is *Staphylococcus aureus*[103]. Infections of the sensitive areas of the body, such as the skull, spine, or sternum, are linked to a high prevalence of morbidity and mortality. In combination with thorough surgical debridement, HBOT is thought to be a viable therapeutic method for refractive osteomyelitis. HBOT can help to reduce infection by activating neutrophils and leucocytes against pathogens and restoring increased oxygen tension in the diseased bone[104, 105]. HBOT treatment sessions vary according on the severity and location of infection. HBOT is normally given for 90-120 minutes at 2-3 ATA over the course of 20-40 sessions, depending on the severity of the infection. The antibiotic treatment should be continued until the debrided bone has revascularized.

6.7 Malignant Otitis Externa

Malignant otitis externa (MOE) is a serious infection of the external auditory canal and temporal bone that usually affects immune-compromised people. The most prevalent pathogen responsible for MOE is *Pseudomonas aerugenosa*, and the degree of infection is determined by the extent of immune-suppression in patients. If left untreated, MOE is highly aggressive and can lead to serious consequences such as cranial nerve damage[106-108]. HBOT at 1.5 ATA, along with a course of antibiotics, has been demonstrated to be useful in reducing infection rates[109, 110]. To limit the chance of infection spreading to the nervous system, many sessions are required over a long period of time (up to 8 weeks).

6.8 Severe Anemia

Anemia develops as a result of acute bleeding, hemolysis, or aplasia, lowering total oxygen carrying capacity and resulting in a rapid deterioration of health[111, 112]. In normal circumstances, 100 milliliters of blood can transport 5-6 milliliters of oxygen to the microvasculature of organ systems. The accumulation of oxygen debt is a measure of the body's oxygen requirement for aerobic respiration. There is an increase in accumulative oxygen debt in anaemic patients. As a result of the decrease in oxygen carrying capacity, the body's oxygen demand cannot be met[113, 114]. To address the rising oxygen debt, a blood transfusion is frequently recommended. When blood transfusion is not possible due to immunological issues, HBOT is a good alternative[115, 116]. To alleviate the complications of severe anaemia, patients can get HBOT at 2-2.5 ATA for up to 3-4 hours. HBOT, whether intermittent or pulsed, enhances oxygen flow to the organs, lowers oxygen debt, and raises overall red blood cell mass.

6.9 Decompression Sickness

Decompression sickness (DCS) is the development of inert gas bubbles as a result of gas supersaturation, which can lead to clinical consequences such as organ failure[117]. DCS is caused by an abrupt drop in ambient pressure, such as when ascending from a dive, in space, or in a hyperbaric/hypobaric chamber. Air bubbles arise when the partial pressure of gases rises above the ambient pressure, causing their dissociation from the blood in the form of bubbles. Joint aches, skin rashes, cardiorespiratory dysfunctions, neurological dysfunctions, and pulmonary edema are all clinical sequelae of DCS[118]. Gradual recompression, which causes a reduction in bubble volume and an increase in the diffusion gradient of air to the surrounding tissue or blood, is indicated as a therapy option for DCS. It also helps to alleviate edema by oxygenating ischemic tissues[119, 120]. To maintain pressure stability, normobaric circumstances are recommended, in which 100 percent oxygen is administered at 1 ATA pressure. For the treatment of severe DCS symptoms, 100% oxygen is administered for 2 hours through a tight-fitting gas mask.

6.10 Intracranial Abscess

An intracranial abscess is a collection of pus caused by bacteria or fungus in the parameninges, such as epidural abscess and subdural empyema. Contiguous infections such as sinusitis, otitis, mastoiditis, and dental infections may be the source of the infection[121]. In comparison to immune-competent patients, those with immune-compromised conditions are more likely to develop cerebral abscess and require a more thorough treatment regimen. In the case of a cerebral abscess, HBOT in combination with antibiotics may be useful[122]. The use of HBOT to treat an intracranial abscess reduces perifocal brain edema by causing vasoconstriction. It also improves the oxidative environment and immune cell infiltration at the abscess site, resulting in antibacterial activity and pathogen phagocytosis[123, 124]. HBOT is given for 60-90 minutes at 2-2.5 ATA pressure for 1-2 sessions each day, however the treatment course can be changed according on the severity of infection and response to treatment.

6.11 Femoral Head Necrosis

Femoral head necrosis is a pathological condition that occurs when the blood supply to the proximal femur is disrupted, resulting in osteonecrosis[125, 126]. Necrosis has undermined the structural integrity of the femoral head, necessitating complete hip replacement in the majority of cases. Femoral head necrosis can be caused by a number of variables, including food, environment, cytotoxicity, and blood disorders such as sickle cell anaemia and haemophilia. Tissue necrosis occurs as a result of a lack of blood supply to the femoral head, causing the trabecular structure of the femur to disintegrate[127]. HBOT can help in femoral head necrosis because osteoblasts become more active in the presence of extra oxygen, allowing them to repair damaged bone structure[128-130]. As a result, HBOT aids in the stimulation of osteoblast activity, which affects the process of bone rebuilding. Edema and related discomfort can also be relieved by a hyperoxygenated state. Furthermore, vascularization of viable bone structures restores blood flow and protects healthy tissues from necrosis.

6.12 Sickle Cell Disease

Sickle cell anaemia is an autosomal recessive disorder characterized by high haemoglobin S (Hb S) concentrations in the erythrocytes. HbS is a variation of normal haemoglobin caused by a point mutation in the globin component gene that causes Glutamic acid to be replaced by Valine. Hb S has a weaker affinity for oxygen and causes sickle cell disease when it accumulates in large concentrations in erythrocytes. RBCs become stiff and sickle-shaped when HbS is present[131, 132]. They can clump together to form huge polymers, obstructing blood arteries. This is known as vaso-occlusion. Because the microvascular network of the organs is obstructed, this produces ischemia injury and pain, which can lead to illnesses including stroke, cognitive impairment, retinopathy, and renal insufficiency[133-135].HBOT has been shown to help patients with sickle cell disease and manage their symptoms. HBOT is known to mimic Nitric oxide synthase, hence increasing NO production. As a result, cell adhesion is reduced, and vaso-occlusion is reduced. In a similar way, HBOT inhibits ICAM-1, which has a protective effect against vaso-occlusion[136-138]. HBOT is used to treat sickle cell disease at a pressure of 2-2.5 ATA. To reverse the clinical symptoms of sickle cell disease, usually just one session is required.

7. Contraindications

HBOT has proven itself as a beneficial modality of treatment in a wide range of clinical disorders during the last few decades[8, 139]. However, in many circumstances, the total applicability and utilization are still insufficient for HBOT to

be universally accepted. HBOT has its own set of contraindications and limits, much like any other clinical procedure. HBOT contraindications are determined by a variety of criteria, including the patient's state, clinical situations, and absolute or relative indications. The development of tension pneumothorax and gas embolism is an unequivocal contraindication to HBOT. During decompression, a pneumothorax might occur, causing the patient to experience rapid variations in pressure. It may be linked to lung barotrauma, which results in pneumothorax, subcutaneous emphysema, or arterial gas embolism. Another essential feature of HBOT to consider is oxygen toxicity, which occurs as a result of the increased formation of oxygen free radicals during the process. From a therapeutic standpoint, elevated free radicals are an important feature of HBOT because it aids in the promotion of oxidative conditions to combat infections. However, in order to avoid the deleterious effects of oxygen poisoning, pO_2 must be constantly monitored. Oxygen poisoning that lasts for a long time can cause neurological, pulmonary, and visual damage. Furthermore, in the event of individuals with co-morbid conditions such as diabetes, lung disease, or neurological problems, particular HBOT procedures must be adopted. Concurrent treatment with some medications, such as bleomycin and doxorubicin, can also aggravate the effect of oxygen toxicity. As a result, the indications for HBOT in the treatment of such individuals should be carefully reviewed. There are a number of other absolute contraindications to HBOT, including unvented pneumothorax and acute severe bronchospasm, which can result in tension pneumothorax and gas embolism as a result of decompression. Due to vasoconstriction, hyperoxic situations can cause cardiac problems such as bradycardia and decreased cardiac output.

Overall, the design and standardization of HBOT protocols for the treatment of various disorders should be based on risk factor assessment and therapy design to achieve maximum therapeutic results while minimizing the risks.

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FIGURES

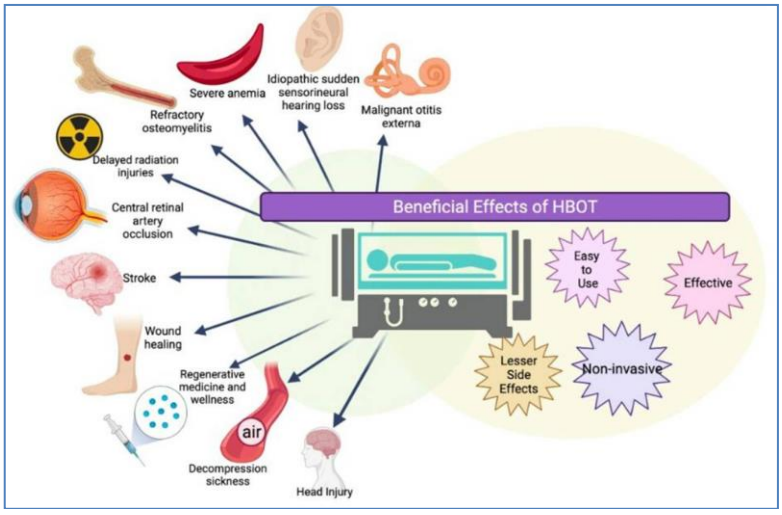

Fig 01- A representative schematic diagram showing the beneficial effects of hyperbaric oxygen therapy (HBOT).

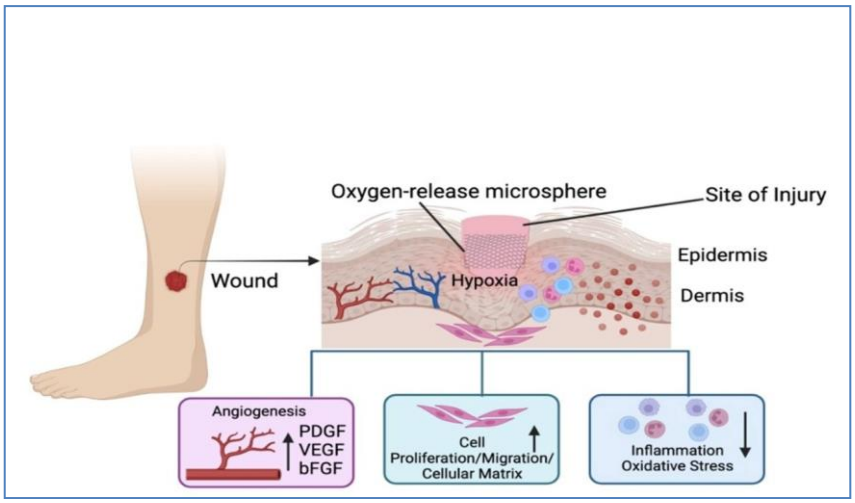

Fig 02 - A representative schematic diagram showing wound healing pathophysiology where cells involved in immunological response, inflammatory response, tissue regeneration, and vascularization response triggered by a hyperbaric environment that causes an increase in cellular activity.

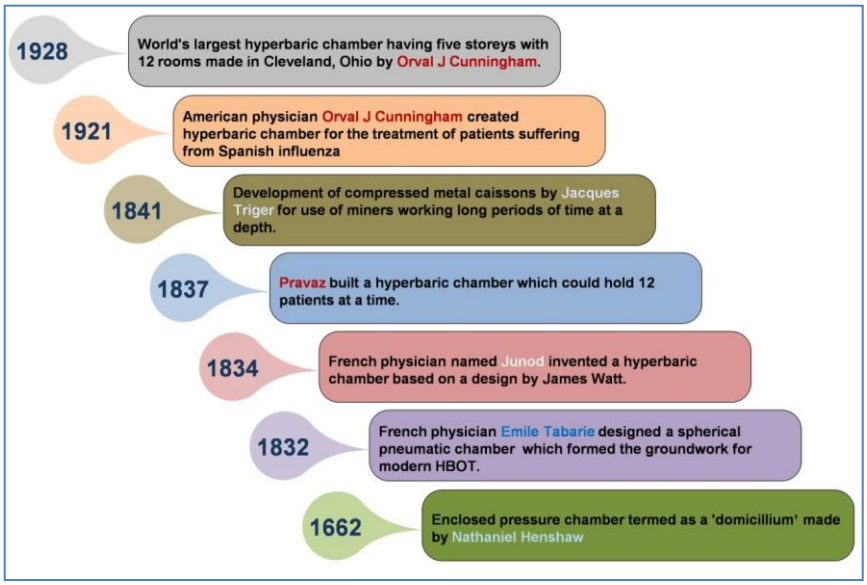

Fig 03- Contributions of various workers in the development of HBOT.

Table 1. Recommended HBOT protocols for various clinical indications

Clinical condition	Recommended HBOT	Treatment frequency
Selected problem wounds	2.0 ATA O_2 for 90 minutes	10 – 40 sessions
Acute thermal burns	2.0 ATA O_2 for 90 minutes	5 – 30 sessions
Compromised skin grafts and skin flaps	2.0 ATA O_2 for 90 minutes	10 – 40 sessions
Osteoradionecrosis	2.5 ATA O_2 for 90 minutes	20 – 60 sessions
Crush injury & compartment syndrome	2.0 ATA oxygen for 90 minutes	3 – 12 sessions
Necrotizing soft tissue infections	2.5 ATA O_2 for 90 minutes	5 – 30 sessions
Non-clostridial gas gangrene	2.5 ATA O_2 for 90 minutes	Above 10 sessions
Radiation tissue damage	2.0 ATA O_2 for 90 minutes	20 – 60 sessions
Refractory osteomyelitis	2.0 ATA O_2 for 90 minutes	20 – 60 sessions
Intracranial abscess	2.5 ATA O_2 for 90 minutes	5 – 20 sessions
Idiopathic sudden sensorineural hearing loss	2 or 2.5 ATA O_2 for 90 minutes	10 – 20 sessions
Central retinal artery occlusion	2 or 2.5 ATA O_2 for 90 minutes	10 – 20 sessions
Clostridial gas gangrene	2.5 ATA O_2 for 90 minutes	2 – 10 sessions
Acute exceptional blood loss anemia	2.0 ATA O_2 for 60-120 minutes	HBO therapy sessions based on patient's clinical condition
Decompression sickness	2 or 2.5 ATA O_2 for 90-120 minutes	Minimum 10 sessions
Carbon monoxide poisoning	2.0 ATA O_2 for 90 minutes	Minimum5sessions
Autism and cerebral palsy	1.8 ATA O_2 for 60 minutes	20 – 40 sessions
Stroke and acute traumatic brain injury	1.8 ATA O_2 for 60 minutes	5 – 20 sessions

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