Hyperbaric Oxygen Therapy for Non-Healing Wounds

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Chronic wounds are a significant challenge to the health care system and its professionals. It has been estimated that 1–2% of the population in the industrial world will suffer from leg wounds that might need professional treatment during their lifetime. In 2001, McGuckin et al. [1] estimated that 3 billion dollars a year are expended for the treatment of leg ulcers in the United States. Moreover, this amount does not include the loss of 2 million working days. In 1994 Lazarus and colleagues [2] defined chronic wound as a wound that fails to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceed through the repair process and stages without establishing a sustained anatomic and functional result. Another way to define a chronic wound is by the healing time, i.e., a wound that does not demonstrate a tendency towards healing after 8 weeks of standard wound care. Other terminologies that are used in the literature for the treatment of difficult wounds include: "non-healing wound," "hard to heal wound," "problem wound" and "chronic cutaneous ulcer."

Hyperbaric oxygen treatment is beneficial in cases where hyperoxygenation improves wound hypoxia

The treatment approach to non-healing wounds is based on three principles: a) treating the main etiology, b) locating and removing the delaying factors, and c) providing the optimal environment for wound healing. Local wound treatment includes: cleansing and debridement, modern wound dressing and innovative treatments for wound healing – such as negative pressure wound treatment, topical growth factors, cultured skin, and macrophages.

Oxygen is an essential component of wound healing, and the rate of healing can be directly linked to the level of tissue oxygenation. According to Mogford and Mustoe [3], wound ischemia is, arguably, the most common cause of wound-healing failure. Hyperbaric oxygen therapy is a treatment for hypoxic wounds. It utilizes oxygen as a drug and the hyperbaric chamber as the mechanical tool for elevating its concentration at the target area. During the treatment, the patient breathes 100% of oxygen, while the surrounding atmospheric pressure is higher than at sea level.

This review article elaborates on the history of HBOT1, the rationale of the physiological treatment, clinical indication and contraindications, patient selection, treatment protocols and side effects.

HISTORICAL BACKGROUND

The first hyperbaric chamber was constructed in London at 1662 by Henshaw [4] and was termed "Domicilium." This chamber compressed room air for treating numerous illnesses such as inflammation, scurvy, arthritis and rickets, yet most likely it had too little compression pressure to induce any physiological effect. Following the discovery of oxygen in the late 1700s by Priestley [5], the development of a pneumatic laboratory enriched with oxygen for the treatment of chronic conditions such as leprosy was established by Beddoes. In 1887 hyperbaric oxygen was first recommended by Valenzuela for the treatment of bacterial infections [6]. The popularity of HBOT was significantly enhanced during the Spanish flu epidemic in 1918, and later as a result of the increased interest in underwater military activities which promoted its use for diving and decompression sickness.

'The golden age' of HBOT began in the late 1950s following the scientific publication by Boerema [7], "Life without blood," in which it was demonstrated that unanesthetized pigs behaved normally with an average hemoglobin of 0.45 g/dl while breathing 100% oxygen in a pressurized chamber of 3 atmosphere absolute. Since the 1970s, more scientifically sound guidelines for the use of HBOT have been formulated, based on prospective randomized controlled clinical trials

HBOT = hyperbaric oxygen therapy

and well-executed basic science studies. The benefits of hyperbaric medicine were subsequently observed for split-thickness skin graft take, flap survival and salvage, acute thermal burns, necrotizing fasciitis infections, chronic wound healing including diabetic ulcers (if adequate vascular inflow is present), hypoxic wounds and radiation injuries.

RATIONALE FOR HBOT FOR NON-HEALING WOUNDS

THE HYPOXIC DAMAGE

Oxygen is essential for intracellular aerobic metabolism. Ischemia/tissue hypoxia (oxygen levels below 30 mmHg) impairs significantly normal metabolic activity and wound healing [8]. Anaerobic metabolism provides insufficient energy for the hypoxic wound [9]. Oxygen is necessary for fibroblast proliferation [10], collagen synthesis, exportation of collagen from the fibroblast cell membrane [11] and neoepithelialization [12].

The extent of wound repair is related to the tissue oxygen concentration [13]. Angiogenesis at the wound's edges is driven by the existing oxygen gradient [14]; the center of the wound has poor oxygenation, whereas the periphery is oxygen rich. This gradient drives macrophages to produce angiogenesis factors until the blood vessel growth towards the wound center is complete. Better oxygen delivery to the wound causes a steep oxygen gradient from the wound edges toward the hypoxic wound center (which is also rich in lactic acid) and subsequently promotes wound repair [15]. Moreover, hypoxia impairs resistance to infection. Bacterial load is higher in hypoxic tissue when compared with hyperoxic tissue [16] since the ability of leukocytes to resist infection is oxygen gradient dependent [17]. High oxygen concentration enhances the ability of leukocytes to produce free radicals, thus causing bacterial death.

In hypoxic wounds an appropriate vascular evaluation and treatment is a prerequisite prior to HBOT

THE PHYSIOLOGY OF HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy involves inhalation of 100% oxygen at a pressure of usually 1.9–2.5 ATA. This therapy results in tissue oxygen levels that are 10 times higher than the usual levels [10]. An intact or only limited damaged regional vascular supply is a prerequisite for oxygen to reach ischemic tissues. The total oxygen content of blood is equal to the hemoglobin-carrying capacity together with the dissolved oxygen content. Under normal conditions, 98% of oxygen is bound to hemoglobin and carried in the bloodstream, while the remaining 2% is dissolved in the plasma.

According to Henry's law (increased solubility of gases in liquid opposed to partial pressure), the increase in the atmospheric pressure magnifies the amount of dissolved oxygen in blood plasma. Breathing 100% oxygen under hyperbaric conditions elevates the arterial pO2 from approximately 100 mmHg, at 1 ATA sea level) to around 1500 mmHg at 2 ATA and up to 2000 mmHg at 3 ATA [8]. The latter is sufficient to supply the tissue with all the metabolic requirements even in the absence of hemoglobin. The dissolved plasma oxygen passes even through partially occluded capillaries, where the passage of red blood cells is limited [18]. The dissolved oxygen content remains in its elevated levels from 2 to 4 hours after HBOT has been terminated [19], which induces the synthesis of endothelial cell nitric oxide synthase. Furthermore, according to Krogh's model [20], when the arterial pO2 is 2000 mmHg (accomplished by breathing 100% oxygen at 3 ATA) the diffusion distance of oxygen increases fourfold.

Other mechanisms by which HBOT promotes oxygen delivery and wound healing include improved red blood cell deformability and flow, reduction of edema and induction of angiogenesis [21].

Beyond the most superficial cell layers, there is no significant topical oxygen diffusion. Thus, delivering additional oxygen to hypoxic tissue must be done systemically, under hyperbaric conditions [22] and not as advocated by other, namely, using topical oxygen therapy.

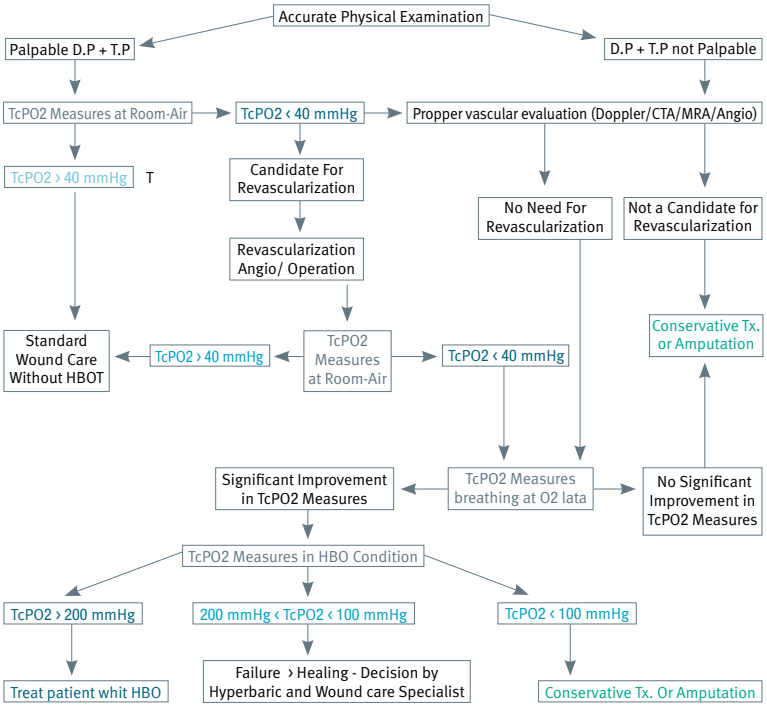
CLINICAL EVIDENCE SUPPORTING HBOT TO TREAT NON-HEALING WOUNDS

The value of hyperbaric oxygenation has been well established in the treatment of hypoxic and ischemic wounds. Several randomized controlled clinical trials [23-27] have demonstrated that HBOT is an effective adjunct treatment for diabetic ischemic foot ulcers and has significantly reduced the incidence of leg amputations. A Cochrane Database Systemic Review [28] concluded that in diabetic patients with foot ulcers, HBOT significantly reduced the risk of major amputation and may improve healing after 1 year. Furthermore, in Canada, adjunctive HBOT for diabetic foot ulcers was found to be cost-effective compared with standard care [29].

The Undersea and Hyperbaric Medical Society and the European Undersea and Baromedical Society indicated that HBOT is an adjunctive treatment for hypoxic non-healing wounds. Medical insurance companies such as The BlueCross/BlueShield and the Agency for Healthcare Research and Quality concluded that there is sufficient evidence to support the adjunctive use of HBO, following revascularization, in the treatment of adequately perfused chronic non-healing-wounds of the lower extremity [30]. The Jury of the Joint Conference on Oxygen and Tissue Repair, established by

ATA = atmosphere absolute

Figure 1. Algorithm: HBOT for patient with non-healing wound



the European Committee for Hyperbaric Medicine and the European Tissue Repair Society recommended in October 2006 [31] that "HBO can be used when standard care fails to achieve oxygen levels necessary for normal wound healing." Furthermore, it has been concluded that "Presently there is reliable evidence that HBO is effective in reducing major amputations in patients with diabetic foot ulcers."

PATIENT SELECTION FOR HBOT

Patients who will benefit from HBOT as adjuvant treatment for non-healing wounds are those who suffer from hypoxic wound with significant improvement of the hypoxia during oxygen breathing at hyperbaric conditions. In order to assess the wound perfusion and oxygenation, an objective method is provided: transcutaneous oxygen pressure. This simple, reliable and non-invasive diagnostic tool can be used for the assessment of tissue perfusion in the vicinity of the non-healing wound. In addition, $TcPO_2$ may be used for the assessment of wound-healing potential, patient selection for HBOT, and in some institutions is used for selection of the amputation level.

Transcutaneous oxymetry is the recommended method for patients with hypoxic wounds who will benefit mostly from adjunctive HBOT

$TcPO_2$ -= transcutaneous oxymetry

Two main questions regarding$TcPO_2$ measurements should be addressed before administering HBOT for non-healing wounds: Is the wound hypoxic, and does the hypoxia improve significantly during HBOT? In answer to the first question, a measurement of $TcPO_2$ lower than 35 mmHg in room air is indicative of tissue hypoxia. Regarding the second question, a measurement of in-chamber $TcPO_2$ of 200 mmHg or more is indicative of a successful HBOT [30]. In rare cases a paradoxical $TcPO_2$ response occurs as a result of severe vasoconstriction, i.e., reduced $TcPO_2$ measurements under hyperbaric conditions. Figure 1 represents an algorithm for hyperbaric oxygen therapy for chronic wounds.

TREATMENT PROTOCOLS

Hyperbaric oxygen treatments for hypoxic wound healing are usually delivered at 1.9–2.5 ATA for sessions of 90–120 minutes each. During the treatment the patient breathes 100% oxygen. A few studies in the literature suggest that higher treatment pressure may not always raise a higher tissue pO_2, probably due to large vessel vasoconstriction as a reaction to hyperoxia.

Treatments are given once a day five to six times a week, as an adjunct to appropriate surgical, medical and topical treatment. Treatments can be continued until the achievement of 100% granulation tissue in the bed of the wound. The average number of treatments is 35 [30], although clinical evidence of wound improvement should be demonstrated after 15–20 treatments [32]. Therefore, the non-healing wound should be reassessed continuously during the entire HBOT regimen by a trained hyperbaric physician together with a wound care specialist.

SIDE EFFECTS

Most side effects of HBOT are mild, and with good nursing are rare; however, more severe side effects should be considered. There are two categories of side effects:

CAUSED BY ATMOSPHERIC PRESSURE CHANGES

The most frequent side effect is middle ear barotraumas, which is expressed in its mild case as hyperemia of the ear drum, demonstrated by painful bulging and accompanied by bleeding to the middle ear in severe cases. Ear drum perforation might also occur. A rare but serious side effect is perilymph leak from the inner ear into the middle ear due to perforation of the oval window [33]. The most serious barotrauma side effect, which is very rare, is lung related, namely, pneumothorax and tension pneumothorax. Only a

few reports have been published, all of which were related to ventilated or comatose patients receiving HBOT [34].

CAUSED BY THE RISE IN OXYGEN PARTIAL PRESSURE

Brain oxygen toxicity was first described by Bert in 1878 [35]. The clinical manifestations are convulsions resembling grand mal seizures, which resolve completely without any neurological deficits after removal of the oxygen mask [36]. Brain oxygen toxicity is pressure dependent and the threshold for immediate toxicity is reached by breathing 100% oxygen at 3.0 ATA. At lower partial pressures, the threshold is time dependent. To avoid oxygen toxicity, planned intervals are utilized during the hyperbaric treatment for air breathing [37]. The incidence of oxygen brain toxicity is estimated to be in one in three cases for 10,000 treatments. These differences are most likely attributed to the range of different treatment protocols in various HBOT facilities.

Oxygen lung toxicity is due to the cumulative damage from oxygen free radicals to lung parenchyma and airways, which is manifested as tracheobronchitis in mild cases and might develop in severe cases to full-blown respiratory distress syndrome. Lung toxicity is time dependent and may occur only in prolonged hyperbaric treatments, which is not the case in the profiles of HBOT for non-healing wounds.

Transient myopia may occur following 40 repetitive HBOT sessions, but is reversed a few weeks after the cessation of treatment.

CONTRAINDICATIONS

There are only a few absolute contraindications for HBOT. The most important is uncontrolled pneumothorax, since it might deteriorate to tension pneumothorax under pressure changes. Other absolute contraindications are current or recent treatment with adriamycin, bleomycin or doxorubicin. The concern is that HBOT may aggravate the cardiac and pulmonary toxicity, but this concern is based on animal studies only. Another contraindication is treatment with disulfiram since it increases the risk of developing oxygen toxicity. Since most of the contraindications are relative, HBOT benefits should be considered versus the risks. Relative contraindications include respiratory infection (might cause sinus and middle ear barotraumas), severe asthma/chronic obstructive pulmonary disease (might cause pneumothorax), high fever (might aggravate the risk of oxygen toxicity), and steroid treatment (aggravates the risk for oxygen toxicity). Other relative contraindications are seizure disorders, pregnancy, not approved implanted pacemaker, history of optic neuritis, and claustrophobia.

Malignancy and even active malignancy is not a contraindication. Moreover, some studies have demonstrated the superiority of HBOT combined with radiotherapy for shrinking tumors [38]. However, it should be kept in mind that skin tumors or skin metastasis may be the cause of non-healing. Therefore, if malignancy in a non-healing wound is suspected, a histopathological biopsy should be taken.

Figure 2. Monoplace chamber

Figure 3. Multiplace chamber

MONOPLACE VERSUS MULTIPLACE CHAMBER

The hyperbaric chamber is the vehicle that enables the hyperbaric condition and there are two types. The monoplace is for a single supine patient [Figure 2]; the chamber is compressed with oxygen and the patient breathes the compressed oxygen from the environment. The multiplace is designed for several patients seated or supine [Figure 3]; the chamber is compressed with air and the patient breathes the compressed oxygen from a

Table 1. text ???????? ??????

Monoplace	Multiplace	
Cost and cost-effectiveness Mobile No need for mask or hood. One-person operation.	Comfortable All patients (including unstable and intubated) Different treatments tables and pressures Medical personnel inside the chamber (to help patient if necessary)	**Advantages**
Only stable and conscious patients Pressure limited Enriched oxygen environment	Cost and cost-effectiveness Large crew needed to operate the machine Not mobile Medical personnel inside the chamber (risk of decompression)	**Disadvantages**

mask or hood. Most multiplace chambers have more than one compartment that serve as an entry lock for personnel to lock in and out of the chamber. The advantages and disadvantages of the two hyperbaric chambers are summarized in Table 1.

CONCLUSIONS

Hyperbaric oxygen is a well-accepted adjuvant treatment for hypoxic wounds and is recommended by different medical societies, health organizations and healthcare agencies. Patient selection for HBOT should be executed carefully and according to accepted guidelines. HBOT should be considered in cases of hypoxic wound (due to ischemia) that demonstrate reversibility of tissue hypoxia under hyperbaric oxygen conditions. Hypoxia and responsiveness to oxygen is measured by $TcPO_2$. The best predictive measure to evaluate the benefit from HBOT for wound healing is $TcPO_2$ values above 200 mmHg in hyperbaric oxygen conditions. HBOT is not indicated for non-hypoxic wounds. Wound caregivers should always keep in mind that HBOT is only an adjuvant treatment. A multidisciplinary approach and optimal topical wound treatment are the cornerstones of wound therapy.

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