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Review Article

Diseases Treated With Hyperbaric Oxygen Therapy; a Literature Review

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ABSTRACT

Hyperbaric oxygen therapy (HBO) is defined as the inhalation of 100% oxygen inside a hyperbaric chamber that is pressurized to greater than 1 atmosphere (Atm). Typical HBO regimens use 1.5 to 2.5 Atm pressure for durations of 30 to 90 minutes, repeated multiple times. The time between and the total number of repeat sessions varies widely. The effectiveness of hyperbaric oxygen therapy for treatment of some diseases such as intravascular emboli, decompression sickness, anaerobic infections, CO poisoning was confirmed. For some diseases, such as traumatic brain injuries, the effectiveness of hyperbaric oxygen therapy as described by investigators is controversial. Chinese authors have reported many articles regarding treatment of neonatal hypoxia with hyperbaric oxygen therapy, but in other points of the world, this depth of experience does not exist. Recently, some other diseases, such as purpura fulminans, and pancreatitis, have been treated by hyperbaric oxygen therapy. In conclusion, if equipment for hyperbaric oxygen therapy is available, many patients will benefit by this method of treatment.

KEY WORDS

Hyperbaric oxygen therapy, diseases, studies.

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INTRODUCTION

Hyperbaric oxygen therapy (HBO) is defined as the inhalation of 100% oxygen inside a hyperbaric chamber that is pressurized to greater than 1 atmosphere (Atm). Typical HBO regimens use 1.5 to 2.5atm pressure for durations of 30 to 90 minutes, repeated multiple times. The elevated pressure of oxygen in these chambers leads to patients showing elevated arterial PO2 and thus improvement of ischemic conditions. The time between and the total number of repeat sessions varies widely in studies (1).

Hemoglobin and nitric oxide independently fulfill diverse and complex physiological roles in the body; together they subtly modulate microvascular perfusion in

response to second-by-second changes in local metabolic demand, contributing to hypoxic vasodilation (2). By increasing tissue PO2 hyperbaric oxygen therapy reverses this phenomenon and induces vasoconstriction by inactivating nitric oxide as a result of increased production of superoxide (3.4).

Venous or Arterial Gas embolism

Gas embolism is well described in the medical literature and nearly always reported as an iatrogenic complication, related to surgery or following trauma. It has been associated with positive pressure mechanical ventilation, the insertion (and removal) of central lines and empty IV infusion set-ups (5,6). It is a known complication of cardiac surgery with an incidence of approximately 0.1%, whether following bypass pump failure or by the introduction of gas in the surgical field. Other described sources of gas embolism include ingestion or colonic irrigation with hydrogen peroxide, and inhalation of pressurized helium. In the gynecologic literature, gas embolism is extensively described as occurring when air is introduced into venous plexuses of the uterus; for example, during douching, illegal abortion, urogenital sex during pregnancy, labor and delivery, laparoscopy, or hysteroscopy with CO2 laser (7). Lastly, it has been increasingly recognized as a complication of serious chest trauma, presumably through the creation of aero-vascular fistulas (8).

The signs and symptoms of gas emboli depend on the amount, nature, and end-position of the introduced gas. Diagnosis is often presumptive, with suggestive signs and symptoms accompanied by a portal of gas entry. Small emboli in skeletal muscle or visceral vessels are usually well tolerated (7). Cerebral, coronary, and pulmonary emboli, however, can result in serious morbidity and mortality. Cerebral embolisms may cause headaches, visual disturbances, altered mentation, weakness, sensory defects, seizures, respiratory arrest, or death. Coronary emboli can cause dysrhythmias, hypotension, and myocardial infarction, whereas pulmonary gas emboli may lead to hypoxia, hypercapnia, and acute respiratory distress syndrome (ARDS) (3,9). Air in the microcirculation can lead to disseminated intravascular coagulation (DIC), tissue ischemia, and gastrointestinal mucosal damage. Physical examination may reveal a “mill wheel” murmur on cardiac auscultation, skin marbling, blanching of the nail beds, pallor of the mucous membranes, or more rarely, air bubbles in the retinal arteries. Echocardiography can be a very useful adjunct in diagnosing intracardiac gas emboli. A head CT scan may reveal subtle changes in cerebral arterial gas embolism, but is not routinely reliable, especially in early diagnosis (10,11). In general, the universally lethal volume of embolized gas in an adult is not known, but is estimated at 200–300 mL of introduced air.

Administration of 100% oxygen, crystalloids infusion, and supportive care are the mainstays of gas embolism therapy. In an effort to decrease cerebral emboli, Trendelenburg positioning is often recommended, as it is thought to decrease the volume of gas “rising” to the cerebral circulation (4,13). More recently, others have recommended flat supine positioning, stressing that Trendelenberg positioning is not only unhelpful in preventing the propulsion of bubbles into cerebral arteries, but may actually aggravate cerebral edema (7,13,14). In aiming to reduce cerebral edema and damage, corticosteroids were previously, but no longer routinely recommended, though various studies have found intravenous lidocaine therapy to be helpful (7,15). Closed chest cardiac massage, in the setting of cardiopulmonary arrest, may also help mechanically with the breakup and dissolution of embolic gas bubbles.

Symptomatic cerebral or coronary air emboli, as suggested in this case, necessitate serious consideration of hyperbaric oxygen therapy (13,16,17). The rationale is based on principles of gas physiology, and this is clinically reinforced. Room air emboli are composed primarily of oxygen and nitrogen. At atmospheric pressure, oxygen readily reabsorbs into solution, but nitrogen remains insoluble and in potentially embolic bubble form. Both high-flow oxygen and hyperbaric oxygen therapy are standard treatments that decrease the size and absorption time of excess bloodstream nitrogen.

“Hyperoxygenation” works not only to oxygenate end organs, but also facilitates the absorption of residual nitrogen. Room air is composed of 80% nitrogen and 20% oxygen, but as the oxygen tension is increased in the blood, the “O2 window” for nitrogen removal is widened. Hyperoxygenation, increasing blood oxygen tension, facilitates nitrogen removal from embolic bubbles by steepening nitrogen bubbles’ downstream gradient into hyperoxygenated (i.e., nitrogen-poor) blood. Clinically, a 4-mm diameter nitrogen bubble disappears in 560 min

on room air, or 56 min on 100% oxygen. Additionally, hyperbaric pressure physically compresses embolic bubbles. Any gas volume varies inversely with ambient pressure (i.e., Boyle's law), thus, at three atmospheres of pressure, a bubble's volume would be but one-third its volume at sea level

Although no formal trials support the use of hyperbaric oxygen in air embolism, well-established pathophysiology and extensive successful clinical experience justify its use as the primary treatment (18). Predictably, the efficacy of hyperbaric therapy is inversely proportional to time elapsed since the embolic event. Benefit is reported when therapy begins several hours after the onset of air embolism (19).

Neonatal hypoxia

The Chinese medical literature may be a rich source of evidence to inform clinical practice and other systematic reviews have also concluded that treatment with hyperbaric oxygen possibly reduces mortality and neurological sequels in term neonates with hypoxic-ischemic encephalopathy (20).

For example, in their study Liu et al. concluded that early HBO treatment with 2 atmospheres resulted in a protective effect against hypoxic-ischemic brain damage-induced long-term brain morphological and histological deficits and spatial learning and memory disability (21).

Additionally, Calvert et al. (22) reported that hyperbaric oxygen (HBO) could be a treatment for neonatal hypoxia-ischemia in a neonatal rat model and could prevent brain injury. In that study, HBO was administered in a chamber for 1 hour at 3 atm (atmospheres), 1 hour after hypoxia exposure. Results suggested that HBO, as a single therapy, is able to attenuate hypoxia-ischemia brain insult and offer neuroprotectivity. The HBO reduced neuronal injury with much less atrophy and apoptosis of immature neurons, resulting in further improvement of sensorimotor function of neonatal brain.

Cerebral ischemia

Clinical and experimental evidence suggests that a localized decrease in oxygen brain tissue availability contributes to the neurological deficit in patients with cerebrovascular disease (CVD) who also present with frontal leukoaraiosis (LA) (periventricular hypodensity on CT scan) and lacunar infarcts. In their study, Vila et al. (23) compared selected patients with symptomatic CVD, LA and lacunar infarcts who received daily exposures to hyperbaric oxygen of 45 min for 10 days with a control of similar patients treated with hyperbaric air. They concluded that there was a statistically significant improvement in all scales for the HBO2 group compared with the placebo group. Neurological improvement persisted in the majority of patients in the HBO group for up to 6 months. Repetition of the HBO2 protocol in 9 patients in whom symptoms recurred after 6 months resulted in improvement of symptoms.

The effectiveness of both normobaric hyperoxia and HBO in experimental transient focal ischemia has been shown by the majority of experimental studies (24–26). In the majority of clinical strokes, however, the occluded vessel fails to reopen rapidly (26)—a setting that is only appropriately reflected in permanent ischemia models.

Velktkamp et al. (27) reported that HBO significantly reduced histological infarct size at 24 h. In their study, 48 Wistar rats underwent filament occlusion of the middle cerebral artery (MCAO). Forty minutes after MCAO, the rats were placed in an HBO chamber and breathed either 100% O2 at 3.0 Atm absolute or at 1.0 Atm for 1 h. Diffusion, perfusion and T2-weighted MR-images were obtained after 15 min and 3, 6 and 24 h of reperfusion. The researchers found that high-dose HBO therapy has an immediate protective effect on the brain that is superior to normobaric oxygen.

Another study by Veltkamp et al. (28) provides several new findings. First, both normobaric hyperoxia and HBO therapy reduced infarct volume in a cortical permanent ischemia model. Remarkably, HBO provided significantly larger protection than normobaric hyperoxia in animal models when started within 120 min after occlusion of the middle cerebral artery. Repeated HBO treatment courses on subsequent days had no additional effect. In contrast, in filament-induced permanent subcortical and cortical ischemia, normobaric hyperoxia and HBO were ineffective, whereas HBO reduced infarct size compared to normobaric hyperoxia in transient filament occlusion of the middle cerebral artery.

Traumatic brain injury

Use of hyperbaric oxygen therapy (HBO) to treat traumatic brain injury is controversial, with implications for clinicians, patients, and health care systems. HBO is

used to treat patients with traumatic brain injury at some hyperbaric centers, but it is not widely accepted as effective for this indication. The potential mechanism of action of HBO in treating traumatic brain injury has not been fully elucidated. Its use in traumatic brain injury is based on the theory that damaged cells are in the ischemic penumbra (the border between healthy and damaged brain tissue), which may have the potential to be recovered (29,30). Improving oxygen availability to these cells may stimulate them to function normally, reactivating them metabolically or electrically, ultimately resulting in angiogenesis and other signs of healing (30). However, the potential for recovery may be diminished as the time postinjury increases (30). This theory is controversial, even though there is evidence that secondary ischemia and oxygen deficiency are important mechanisms of cell death in traumatic brain injury (31).

Studies in humans showing improvements in blood flow to injured areas, as documented by serial single proton emission computed tomography scans, and changes in cerebral metabolism in patients with traumatic brain injury after HBO help to support this theory (30–33).

The evidence is insufficient, however, to prove the effectiveness or ineffectiveness of HBO for traumatic brain injury, and other high-quality studies are needed (34).

Cardiac ischemia

Normobaric therapy has been in use for many years in the treatment of ischemic heart disease (35). When oxygen is breathed in concentrations higher than those found in the atmospheric air, it is considered to be a drug. A limited amount of oxygen is dissolved in blood at normal atmospheric pressure, but under hyperbaric conditions it is possible to dissolve sufficient oxygen, for example 6%, in plasma to meet the usual requirements of the body. The oxygen physically dissolved in solution will be utilized more readily than that bound to hemoglobin, and this effect may normalize or increase oxygen tension in ischemic tissue (35).

The role of HBO in patients with acute myocardial infarction is debatable, ranging from no beneficial effect (36,37) to a favorable effect (38,39). The only controlled trial was completed by Thurston et al. (38) in the prethrombolytic area and revealed a trend, but not a statistically significant decrease, in mortality rates especially in high-risk patients. An animal study conducted by Thomas et al. (39) proved the hypothesis that a combination of thrombolytic therapy and HBO would be more effective in reducing the size of the myocardial infarction than either of these modalities alone. Therefore, a randomized pilot trial conducted by Shandling et al. (40) demonstrated that adjunctive treatment with HBO appears to be feasible and safe for patients in the acute phase of myocardial infarction. Finally, the Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction study (41) demonstrated that treatment with HBO in combination with thrombolysis might result in an attenuated creatine phosphokinase rise, more rapid resolution of pain, and improved ejection fraction (42).

The effect of hyperbaric oxygen therapy on the bout of treatment for soft tissue infections

Tissue oxygen tensions are affected mainly by the concentration of inspired oxygen, cardiac output, local blood flow, cellular metabolism and substrate availability (43). Partial pressures of oxygen (PO2) are normally different in various body compartments. When the PO2 in normal and infected tissues were measured with an oxygen microelectrode, dramatic decreases were found at the site of infection (44). A critical step in the killing of bacteria by polymorphonuclear neutrophils (PMN) is the production of H2O2; however, the ability of the PMN to produce H2O2 is decreased under anaerobic conditions (45). Hohn showed that the killing efficiency of human neutrophils for Staphylococcus Aureus was impaired by PO2 levels below 15 mmHg and severely decreased at levels from 5 to 0 mmHg (46). The decrease in tissue PO2 from the normal 60 mmHg to less than 10 mmHg corresponds with the influx of leukocytes (44). The aim of HBO is to increase transported oxygen in the blood by increasing the physiologically dissolved oxygen. Furthermore, increased local PO2 is sufficient to influence bacterial killing by neutrophils and HBO has been shown to increase the killing ability of neutrophils (47–49).

Studies have demonstrated that HBO therapy has bacteriostatic and bactericidal activity (50). Hyperoxia increases free-radical production and the increase of super oxide induced by HBO is toxic to both anaerobic and aerobic bacteria (43). Mader demonstrated that HBO alone was as effective as an antibiotic in the treatment of

experimental osteomyelitis due to Staphylococcus Aureus in rabbits (51).

Additionally, HBO improves wound oxygenation so that host factors are able to control infection and function to heal the wound. Collagen synthesis in wounds is accelerated by exposure to moderate hyperoxia. Hunt showed the oxygen dependency of collagen production by fibroblasts (52). In another experimental study (53), HBO therapy has been shown to reduce skeletal muscle edema and necrosis in rat hind limb tourniquet ischemia, and in dog hind limb compartment syndrome models. In several mechanisms, HBO can enhance the effect of antibiotic therapy. In conclusion, HBO therapy combined with antibiotic therapy for soft tissue infections is recommended.

There was also a clear clinical correlation between O2 availability via a face mask and the development of wound infection. A study by Grief et al. (54) provided additional clinical evidence that enhancing wound O2 levels through the administration of supplemental O2 can improve the host's immune responses. In their study of 500 patients undergoing abdominal surgery, all of whom received prophylactic antibiotics, administration of O2 at an 80% FiO2 during surgery and for 2 hours postoperatively resulted in a 5.2% wound infection rate versus an 11.2% infection rate in patients given O2 at a 30% FiO2 (54).

Treatment of acute carbon monoxide poisoning

The guideline 'Treatment of acute carbon monoxide poisoning' from doctors in clinics with a tank for hyperbaric ventilation shows that carbon monoxide (CO) poisoning is a potentially life-threatening emergency. Its prognosis is linked to prompt recognition and treatment. CO is toxic because it binds to hemoglobin (Hb), thus impairing oxygen transport and causing tissue hypoxia. The most important symptoms are headache and altered consciousness, ranging from somnolence to coma. The diagnosis is based on a history of CO exposure combined with an elevated carboxyhemoglobin (HbCO) level in the blood. On the basis of the available literature, it is recommended that patients with an HbCO level > or = 10% should always be treated. In patients requiring artificial ventilation, 100% oxygen for 8 hours is recommended. In pregnant women and in patients who are or have been comatose, hyperbaric oxygen can be considered. In all other symptomatic patients, use of a non-rebreathing mask with 100% oxygen for 8 hours is recommended (55).

Recently, a large prospective study showed that hyperbaric oxygen improves the results of neuropsychological testing in all CO-poisoned patients, regardless of their consciousness level (56). In CO-poisoned rats without loss of consciousness hyperbaric oxygen therapy was superior to normobaric oxygen in improving survival time, survival rate and reducing neurological morbidity (57,58). These acute effects of hyperbaric oxygen could be the result of reducing brain edema (57–58).

Burns

Hyperbaric oxygen therapy (HBO) can be used as an intervention for burns therapy. It was first suggested for the treatment of thermal burns more than 40 years ago when Wada et al. (59) serendipitously observed more rapid healing of second-degree burns in a group of coal miners who were being treated with HBO for carbon monoxide poisoning. In 1969, Gruber et al. (60) demonstrated that the area sub-adjacent to a full-thickness injury was hypoxic and could be raised to normal or supra-normal levels through the administration of oxygen under pressure. This was followed by a series of animal experiments that demonstrated a significant reduction of edema, improved microcirculation, reduced inflammatory responses, faster epithelialization, and improved wound healing with HBO (61,62).

The modest increase in tissue oxygen tension enables a raft of immune and healing functions in the hypoxic tissue. For example, the process of phagocytosis involves consumption of oxygen in an 'oxidative burst' and although such processes are possible at remarkably low tissue oxygen tensions, improving oxygenation to within or above the physiologic range dramatically improves the efficiency of such activity. Allen et al. (63) has shown that oxygen tensions between 40 and 80 mmHg are required to maintain activity at 50% of maximum in the NADPH-linked oxygenase responsible for this respiratory burst. For it to work at 90% of maximum, oxygen tension of 400 mmHg may be required (63).

In summary, while there is insufficient evidence to recommend routine HBO in the care of thermal burns, there appears to be a case for appropriate clinical investigation of this interesting treatment modality (64).

Pain treatment

Kiralp et al.'s study aimed to assess the effectiveness of hyperbaric oxygen (HBO) therapy for treating patients with complex regional pain syndrome. In the group that received 15 sessions of hyperbaric oxygen therapy there was a significant decrease in pain and edema and a significant increase in the range of motion. They concluded that HBO is an effective and well-tolerated method for decreasing pain and edema and increasing the range of motion in patients with complex regional pain syndrome (65).

A review by Yidiz et al. (66) concluded that HBO may be beneficial if appropriate patients are selected for treatment of fibromyalgia syndrome (67), complex regional pain syndrome, myofascial pain syndrome, migraine, and cluster headaches (66).

Other diseases treated with HBO

There are a wide range of conditions where hyperbaric oxygen therapy is used in addition to traditional methods for treatment of other diseases. These include acute intoxications by psychotropic drugs (68), prevention of leakage from colonic anastomoses (69), treatment of infected free bone transplants (70), purpura fulminans (71), treatment for malabsorption in radiation-damaged short bowel (72), and in the treatment of nephrotic syndrome (73). In addition, it has been reported in the treatment of radiation injuries in gynecological cancers (74), for improving cardiac neural regulation in patients with diabetic autonomic dysfunction (75), for hepatic artery thrombosis following liver transplantation (76); as well as for necrotizing fasciitis (77,78), bacterial endocarditis (79), after microsurgical repair of transected peripheral nerves (80), and for managing pyoderma gangrenosum (81). More specific conditions include ischemic scleroderma wounds (82), radiation-induced proctopathy (83), bacterial brain abscesses (84), idiopathic sudden sensorineural hearing loss and tinnitus (85), cirrhosis (86), malignant otitis externa (87), lymphedema after breast cancer treatment (88), radiation-induced non-healing wounds (89), and Fournier gangrene (90) among other diseases.

CONCLUSION

This review has shown that if equipment for hyperbaric oxygen therapy is available, there are many patients who would benefit from treatment by this method.

DISCLOSURE

Conflicts of Interest: None declared.

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