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Hyperbaric Oxygen in the Treatment of Patients With Cerebral Stroke, Brain Trauma, and Neurologic Disease

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ABSTRACT

Hyperbaric oxygen (HBO) therapy has been used to treat patients with numerous disorders, including stroke. This treatment has been shown to decrease cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, and maintain blood–brain barrier integrity. In addition, HBO therapy attenuates motor deficits, decreases the risks of sequelae, and prevents recurrent cerebral circulatory disorders, thereby leading to improved outcomes and survival. Hyperbaric oxygen also accelerates the regression of atherosclerotic lesions, promotes antioxidant defenses, and suppresses the proliferation of macrophages and foam cells in atherosclerotic lesions. Although no medical treatment is available for patients with cerebral palsy, in some studies, HBO therapy has improved the function of damaged cells, attenuated the effects of hypoxia on the neonatal brain, enhanced gross motor function and fine motor control, and alleviated spasticity. In the treatment of patients with migraine, HBO therapy has been shown to reduce intracranial pressure significantly and abort acute attacks of migraine, reduce migraine headache pain, and prevent cluster headache. In studies that investigated the effects of HBO therapy on the damaged brain, the treatment was found to inhibit neuronal death, arrest the progression of radiation-induced neurologic necrosis, improve blood flow in regions affected by chronic neurologic

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disease as well as aerobic metabolism in brain injury, and accelerate the resolution of clinical symptoms. Hyperbaric oxygen has also been reported to accelerate neurologic recovery after spinal cord injury by ameliorating mitochondrial dysfunction in the motor cortex and spinal cord, arresting the spread of hemorrhage, reversing hypoxia, and reducing edema. HBO has enhanced wound healing in patients with chronic osteomyelitis. The results of HBO therapy in the treatment of patients with stroke, atherosclerosis, cerebral palsy, intracranial pressure, headache, and brain and spinal cord injury are promising and warrant further investigation.

Keywords: hyperbaric oxygen; stroke; pain; migraine; cerebral palsy; spinal cord; brain injury

INTRODUCTION

Hyperbaric oxygen (HBO) therapy is delivered by a procedure in which 100% pure oxygen is administered at greater than atmospheric pressure. HBO therapy chambers were developed at the turn of the 19th century for the purpose of administering HBO to caisson workers and deep-sea divers with decompression sickness. Treatment is administered within a monoplace chamber that houses 1 patient placed in the supine position, or it may be given in a multiplace chamber that accommodates 2 or more patients. The procedure is safe and is associated with few adverse effects. Central nervous system and pulmonary toxic effects are rare but include seizures, visual changes, sweating, muscle twitching, cough, pulmonary fibrosis, and shortness of breath. The most common and easily managed complication is barotitis, which can lead to episodes of barotrauma, such as rupture of the tympanic membrane or middle ear and sinus injury.[1]

HBO stimulates angiogenesis and neovascularization, optimizes cellular oxygen levels, promotes osteoblast and fibroblast proliferation and collagen formation, and supports the growth of new blood vessels. HBO is often administered to promote proliferation of fibroblasts, epithelial cells, and blood vessels in nonhealing wounds. It can also enhance the killing ability of leukocytes and may inhibit toxin production by certain anaerobes, while exerting direct bactericidal effects. This therapy is administered to increase the flexibility of red cells, reduce tissue edema, preserve intracellular adenosine triphosphate, and maintain tissue oxygenation in the absence of hemoglobin.

In addition to its administration for decompression sickness, the Undersea and Hyperbaric Medical Society has approved the use of HBO for several other conditions, including burns, gas gangrene, soft tissue infection, skin graft, bone infection, intracranial abscess, anemia and blood loss, crush injury, carbon monoxide poisoning, radiation complications, and air and gas embolism. Evidence shows that HBO increases tumor oxygenation and improves the response of many solid tumors to radiation therapy. HBO has been used to treat patients with delayed radiation injuries in soft tissue and bone, as well as those with symptomatic radiation reactions in the urinary bladder and bowel, laryngeal radionecrosis, and radiation-induced optic neuropathy, proctitis, and necrosis of the brain. HBO therapy also enhances sensitivity to chemotherapy. A significant improvement in tumor response was obtained when photodynamic therapy was delivered during hyperoxygenation.[2] Since the early 1960s, many laboratory and clinical studies have reported that HBO therapy has a beneficial effect

in the treatment of patients with complications related to heroin overdose, arthritis, multiple sclerosis, cyanide poisoning, autism, stroke, chronic fatigue, allergy, senility, cirrhosis, and gastrointestinal ulcer.[3,4] HBO was found to be effective in the management of various pathologic conditions of the nervous system (Table 1).

This article reviews important publications regarding the physiologic and clinical influence of HBO on nervous system disease. The proposed mechanism of action of HBO in the management of these conditions is summarized in Table 2.

Table 1. Neurologic Diseases Treated With Hyperbaric Oxygen

Stroke
Lower limb ischemia
Cerebral palsy
Increased intracranial pressure
Migraine headache
Brain injury
Radiation-induced necrosis
Hydrocephalus
Spinal cord injury
Pain, such as exercise-induced muscle soreness, decompression sickness, fibromyalgia syndrome, and complex regional pain syndrome
Atherosclerosis

Table 2. Proposed Mechanisms of Action of Hyperbaric Oxygen in the Treatment of Patients With Neuronal Disease

Inhibits leukocyte activation and infiltration
Inhibits cyclooxygenase-2 expression
Decreases cerebral edema
Reduces lipid peroxidation
Increases oxygen level at neuronal tissues
Relieves intracranial pressure
Decreases immunoreactivity of substance P
Increases level of glutathione and induces expression of antioxidant enzymes
Suppresses proliferation of macrophages and foam cells in atherosclerotic lesions
Reduces ischemia-reperfusion injury
Accelerates tissue wound healing

HYPERBARIC OXYGEN THERAPY FOR NERVOUS SYSTEM DISEASE

Stroke

Ischemia of the Brain

Stroke is the third leading cause of death and the leading cause of long-term disability in the United States. Approximately 80% of all strokes are ischemic, and available therapies approved for the treatment of patients with acute ischemic stroke are limited. For a large number of patients with stroke, no therapeutic option outside of thrombolytic therapy can be offered. Numerous animal and human investigations have shown that once stroke occurs, the risk of neuronal injury is increased by hypoxia, hyperglycemia, hypotension, pyrexia, and dehydration. For patients with acute stroke, stability of blood pressure, glucose level, temperature, hydration, and oxygen saturation is critical if neuronal injury is to be reduced and functional outcome and survival improved. In cerebral ischemia, local anoxia leads to cellular damage and ultimately to complete stroke. The goal of any therapy for patients with acute ischemic stroke is to salvage structurally normal tissue, which is at risk for irreversible damage. Usually, cerebral hypoxia is a major component of immediate and secondary cell damage caused by ischemia. In such cases, therapy should focus on improving blood flow in occluded blood vessels and enhancing cellular and metabolic function.

In ischemic events such as stroke, HBO therapy has been to shown to promote oxygen delivery; inhibit leukocyte activation; decrease cerebral edema, lipid peroxidation, and severity of brain infarction; improve outcomes; and maintain blood–brain barrier integrity.[5-12] The severity of damage caused by chronic ischemic changes in the brain can be reduced by HBO, after which subsequent extra-intracranial arterial bypass surgery can further facilitate recovery.[13] HBO therapy has demonstrated value as adjunctive treatment in patients with ischemic cerebral stroke, including those who have undergone surgery on the extracranial portion of the cerebral major vessels.[14]

In a study of patients with increased water volume in the brain caused by focal brain ischemia, a short course of HBO treatment normalized water volume.[15] In another study, HBO therapy, administered immediately or 60 minutes after reperfusion, significantly reduced cerebral infarction and motor deficits.[16] In other patients who were given HBO therapy at 3 atmospheres absolute (ATA), infarct volume was reduced when oxygen supply to the ischemic periphery was increased without aggravation of lipid peroxidation.[7] In animals administered HBO, the infarct volume measured 24 hours after onset of focal cerebral ischemia was significantly reduced (18%). In rabbits, treatment with HBO after the occurrence of global cerebral ischemia increased free radical concentration in the brain. When measured after 75 minutes of recirculation, this increase was not associated with increased lipid peroxidation or inhibited neurophysiologic recovery. Therefore, HBO administered immediately after global ischemia occurs does not promote early brain injury.[17]

Animal Experimentation

In rat models of cerebral ischemia, HBO administered early after global cerebral ischemia reduced infarct size and increased survival.[18,19] As shown by magnetic resource imaging, the neuroprotective effects of treatment began 5 hours after the ischemia began and were maintained for 5 days without significant oxidative damage. In addition, at 3 to 5 hours after the ischemic event, magnetic resource imaging revealed a smaller ischemic lesion. In another animal study, HBO treatment reduced the infarct area and improved neurologic scores 7 days after reperfusion.[20] Results of a rat study suggest that the neuroprotective effects of HBO in cerebral ischemia may involve the inhibition of polymorphonuclear neutrophil infiltration in the injured brain.[21]

In 2 rat models of acute cerebral ischemia (transient or permanent focal ischemia), treatment with HBO was highly efficacious in reducing infarct volume and improving neurobehavioral outcome within the first 6 hours in rats with transient middle cerebral artery occlusion.[22] At later time points (≥12 hours), however, treatment increased infarct volume. It is interesting to note that HBO treatment is able to attenuate the effects of hypoxia or ischemia in the neonatal rat brain by reducing the progression of neuronal injury and enhancing sensorimotor function.[23]

Other rat studies have shown that the neuroprotective effects of HBO treatment are enhanced when treatment is administered early after an ischemic event.[24] Hyperoxia within 30 minutes of the event significantly reduces total and cortical lesion volumes at 48 hours after stroke. In rats subjected to transient stroke, 100% oxygen administered within 30 minutes after the event salvaged ischemic brain tissue, especially in the cerebral cortex. In a middle cerebral artery occlusion/reperfusion model, treatment with HBO at 6 hours after reperfusion significantly reduced the infarct area to less than that in animals not given the treatment.[25] The neuroprotective effect of HBO involves inhibition of cyclooxygenase-2 overexpression in the cerebral cortex.[25] Moreover, studies have shown that treatment with HBO prior to ischemia or during middle cerebral artery occlusion significantly reduces polymorphonuclear neutrophil infiltration, thus reducing brain injury, motor disorders, and cerebral infarction volume.[26] HBO can also improve outcomes when administered early after temporary focal ischemia.[27] It has been shown to reduce the expression of hypoxia-induced factor 1α, vascular endothelial growth factor, and BNIP3; alleviate neuronal damage; and improve cortical cerebral blood flow and neurologic function in subarachnoid hemorrhage. It is believed that HBO reduces early brain injury after subarachnoid hemorrhage by inhibiting hypoxia-induced factor 1α and its target genes, thereby reducing apoptosis and preserving blood–brain barrier function.[28]

Clinical Studies

In a study of 122 patients with stroke caused by acute and complete thrombosis, HBO therapy was administered as adjunctive therapy with conventional therapy of stroke, and the authors recommended that treatment be provided at 1.5 to 2 ATA.[29] In another study involving 22 patients with cerebral infarction secondary to occlusion of a carotid or middle cerebral artery who were administered HBO at 1.5 ATA, 10 patients demonstrated improved motor function during therapy.[30] Of these patients,

7 underwent successful surgical revascularization without subsequent recurrence of neurologic deficit. In 124 patients in the acute stage of ischemic stroke, HBO therapy prevented the development of recurrent cerebral circulatory disorders and reduced the incidences of some complications, such as pneumonia, pulmonary edema, and thromboembolism of the pulmonary artery.[27,31] Another study showed that patients with acute cerebral stroke treated with HBO demonstrated no recurrent impairment of the cerebral circulation during the acute period.[32]

In a study of 124 patients with central nervous system dysfunction caused by atherosclerosis and essential hypertension, 60 presented with initial manifestations of cerebral circulation insufficiency, 33 with posthypoxic encephalopathy, and 31 with ischemic stroke.[33] Patients with cerebral circulation insufficiency and posthypoxic encephalopathy benefited from a short course of HBO (administered at 1.2–1.25 ATA in as many as 3 sessions), as did those in the acute stage of ischemic stroke, who received HBO at 1.4 ATA in combination with heparin therapy.[33] Hyperbaric oxygen therapy has been reported to be effective in treating patients with Binswanger's disease and hemorrhagic stroke.[34,35] In 1997, Nighoghossian and Trouillas observed that among more than 400 cases of human ischemic stroke treated with HBO that had been reported up to that time, about half demonstrated clinical or electroencephalographic evidence of improvement.[36] These investigators concluded that HBO therapy may be a safe method for improving outcomes after stroke.[37]

Despite many studies that have addressed the use of HBO in the treatment of patients with stroke, the effectiveness of HBO in clinical and experimental acute ischemic stroke has been controversial. Although HBO has been used frequently in the treatment of patients with cerebral ischemia, the Alternative Therapy Evaluation Committee for the Insurance Corporation of British Columbia has suggested that the medical literature does not support the use of HBO for traumatic brain injury and stroke,[38] pointing out that no studies have addressed the dose-related effects of HBO therapy in patients with acute ischemic stroke. Another review, however, has demonstrated that the efficacy of HBO therapy tends to increase as the dosage increases.[39] Clearly, previous studies have demonstrated promising results—strong enough to warrant further clinical study of HBO therapy in patients with stroke.

Atherosclerosis

Oxidized lipoproteins are well-documented causative factors in atherosclerosis. For example, a major consequence of the peripheral accumulation of cholesterol is the oxidation of cholesterol-rich lipoproteins, such as low-density lipoprotein. It has been proposed that arterial wall hypoxia is linked to risk factors that lead to atherosclerosis. The primary mechanism is decreased oxygen delivery resulting from a microcirculatory derangement caused by impaired erythrocyte deformability.[40]

Hyperbaric oxygen increases the serum glutathione concentration and induces the expression of a number of antioxidant enzymes in tissues,[41-43] including heme oxygenase,[36,38] which was recently shown to inhibit the development of atherosclerosis and to slow the accumulation of oxidation in high-density lipoprotein.[44,45]

Repeated exposure to HBO may induce the production of antioxidant enzymes/reagents in tissues such as the arterial wall, thereby inhibiting the formation of oxidized lipoproteins and atherosclerosis.[41,46] Furthermore, in rabbits, repeated short exposure to HBO induces an antioxidant defense mechanism that is responsible for

retarding the development or accelerating the regression of atherosclerotic lesions.[47] Treatment with HBO markedly reduces the accumulation of lipid oxidation products in plasma, in the low-density lipoprotein and high-density lipoprotein fractions of plasma, in the liver, and in the aortic tissues. In addition, HBO treatment prevents the decrease in plasma paraoxonase activity that was observed in rabbits fed cholesterol-rich diets. Moreover, HBO therapy accelerates the regression of preestablished atherosclerotic lesions. It is interesting to note that HBO suppresses the proliferation of macrophages and the formation of foam cells in atherosclerotic lesions.[47]

In a study of 70 patients with obliterating disease of the blood vessels, those who received HBO in combination with magnetotherapy went into remission for 1 to 2 years, whereas those who received HBO therapy alone went into remission for 3 to 8 months. A prolonged positive effect was demonstrated in 64 patients.[48] Hyperbaric oxygen, sympathetic block, and warfarin therapy were administered to promote peripheral tissue circulation in patients with ischemia in the extremities and diabetes mellitus; these methods were very effective for the treatment of patients with intractable injury involving severe necrosis.[49] In a study of 123 patients with ischemia of the lower extremities caused by atherosclerosis, the best outcomes were achieved with a combination of drugs and HBO therapy.[50]

Cerebral Palsy

Cerebral palsy is a disorder of the developing brain that affects the motor system and may be associated with epilepsy and abnormalities of speech, vision, and intellect. Evidence suggests that most cases are caused by intrauterine insult or structural abnormalities of the central nervous system.[51,52] Other than supportive management, no medical treatment is available for patients with cerebral palsy. New alternative approaches to treating patients with cerebral palsy, such as HBO, conductive education, the Adeli suit, and therapeutic (subthreshold) electrical stimulation, were addressed in a recent review that presented controversial results.[53] In an animal study involving 7-day-old pups subjected to cerebral ischemic hypoxia, HBO treatment attenuated the effects of hypoxia on the neonatal brain by reducing the progression of neuronal injury and enhancing sensorimotor function.[20] In a study of 25 children with a functional diagnosis of spastic diplegic cerebral palsy, those who underwent HBO therapy demonstrated improved gross motor and fine motor function, along with reduced spasticity.[54]

Papazian and Alfonso reviewed a series of studies, case reports, and letters published between 1996 and 2003 that addressed the use of HBO in cerebral palsy.[55] In the 1 controlled study that they reviewed, all 75 children with spastic diplegic cerebral palsy who had undergone 40 one-hour HBO therapy sessions (at 1.75 ATA) or sham treatment (normal air at 1.3 ATA) for 2 months demonstrated similarly reduced spasticity and significant improvement in gross motor function, fine motor control, self-control, auditory attention, and visual working memory during most of the study and at 3 months afterward.[56] Although data supporting the use of HBO therapy for patients with cerebral palsy are lacking, and much of the evidence has been anecdotal, these results suggest that more controlled studies are necessary to define the role of HBO therapy in patients with cerebral palsy for whom standard pharmacologic therapy is ineffective.

Intracranial Pressure

Excessive intracranial pressure is caused by increased cerebrospinal fluid pressure or lesions or swelling within the brain matter itself. Many conditions, such as head injury, brain tumor, hypertensive brain hemorrhage, stroke, inflammation, and hydrocephalus, can increase intracranial pressure.

The effects of HBO on brain circulation and oxidative stress were studied in dogs subjected to 18 minutes of complete cerebral ischemia.[57] At 120 minutes after HBO was administered, intracranial pressure was reduced significantly and cerebral blood flow did not change significantly. Results showed that treatment with HBO was effective in reducing brain damage after complete cerebral ischemia, without increasing oxidative stress. In a clinical study involving patients who had received HBO therapy, changes in intracranial pressure, heart rate, arterial blood pressure, and transcutaneous partial pressure of carbon dioxide or oxygen (PO_2) were recorded continuously as patients were administered normal air or 100% oxygen at 1.0 to 2.5 ATA.[58] Heart rate and transcutaneous partial pressure of carbon dioxide decreased and mean arterial blood pressure was unchanged during HBO inhalation. Intracranial pressure decreased initially after therapy began but increased gradually during the treatment period. In a study of the effects of hyperbaric conditions on oxygenation, intracranial pressure, and glucose/lactate levels in the brain in healthy non–brain-traumatized animals, a fraction of inspired oxygen level of 1.0 led to a significant increase in brain oxygen tension.[59]

In intratumoral and peritumoral tissue (eg, glioblastoma), the PO_2 has been observed to rise and remain elevated 15 minutes after administration of HBO therapy. The PO_2 level in peritumoral tissue may be affected by intracranial pressure.[60] It is interesting to note that HBO therapy can improve the clinical outcome and cerebral function of severely brain-injured patients by reducing intracranial pressure, which in turn reduces the risks of cerebral vascular spasm, cerebral ischemia, and hypoxia.[61] In a controlled study of 166 brain-injured patients, of whom 84 were given HBO therapy and 82 were control subjects, mortality after 12 months was 17% among those given HBO therapy and 32% among control subjects. In an analysis of 87 patients with peak intracranial pressure >20 mm Hg, mortality was 21% among those given HBO therapy versus 48% in the control group.[62]

In a study that addressed carbon monoxide poisoning, investigators found that the cerebrospinal fluid pressure associated with acute carbon monoxide poisoning was related to left hemispheric edema, and that cerebellar herniation was the predominant cause of death after carbon monoxide exposure. Among patients exposed to carbon monoxide in this study, HBO but not normobaric oxygen therapy prevented severe increases in cerebrospinal fluid pressure and reduced mortality after exposure.[63] In another study, 8 patients with elevated intracranial pressure underwent HBO treatment with 100% oxygen at 2 ATA per day for 15 days, during which signs and symptoms of the disorder were gradually resolved in all patients.[64]

HBO therapy can be effective in reducing intracranial pressure by decreasing cerebral blood flow. The ability of HBO to increase cerebral oxygenation concomitantly suggests its applicability for the treatment of patients with traumatic cerebral edema, as revealed by the results of a study that included 50 patients administered HBO at 2 ATA.[65] In another study, myringotomy performed to reduce pain during

HBO therapy appeared to reduce intracranial pressure.[66] In a prospective randomized trial of severely brain-injured patients, HBO therapy decreased intracranial pressure 1 to 6 hours after treatment and reduced mortality by 50%.[67]

Headache

Migraine is one of the most common medical disorders, and the search for relief continues. Early treatments for patients with migraine included inhaled 100% oxygen. Increased oxygen in the blood is thought by some to act as an α-adrenergic agent in alleviating headache pain through vasoconstriction and local metabolic effects. The standard treatment for patients with acute cluster headaches is inhalation of 100% oxygen. In the prophylaxis of episodic cluster headache, ergotamine, verapamil, lithium, serotonin inhibitors, and steroids are used. In chronic cluster headaches, lithium is the drug of choice, but verapamil also may be effective.[68-71] In recent studies, HBO provided immediate relief of acute attacks and showed promise in prophylactic treatment.[72,73]

The first reported case of cluster headache syndrome treated with HBO appeared in 1989 and involved a patient with severe cluster headaches who underwent treatment in a hyperbaric chamber on 2 occasions.[73] Her symptoms had been refractory to other treatments, including conventional oxygen therapy. On both occasions, pain was promptly relieved after the patient breathed 100% oxygen administered at 2 ATA. In a study involving 16 patients, 12 patients with episodic headaches and 4 with chronic cluster headaches received active treatment with 100% oxygen (administered at 250 kPa [2.5 ATA]) or placebo (10% oxygen in nitrogen) for 70 minutes in a multiplace hyperbaric chamber; treatment was provided in 2 sessions that occurred 24 hours apart. In all, 83% of patients with episodic cluster headaches and 25% of those with chronic cluster headaches responded to 1 of the 2 treatments, as indicated by a 50% or greater reduction in headache index score, or by remission. The hyperbaric condition itself seemed effective in reducing the headache index score—at least in patients with episodic cluster headaches.[74]

In another study, women with confirmed migraine were randomly assigned to receive control treatment (nonpressurized 100% oxygen) or hyperbaric treatment (pressurized 100% oxygen). Both treatments resolved muscle tenderness and edema, but only pressurized oxygen relieved the subjective pain associated with migraine headache.[75]

In another study, 20 migraineurs were randomly assigned to receive in a hyperbaric chamber 100% oxygen given at 1 ATA (normobaric) or 100% oxygen given at 2 ATA (hyperbaric) for the treatment of a typical headache attack. Only 1 of 10 patients in the normobaric group reported significant relief of headache symptoms, whereas 9 of 10 in the hyperbaric group found relief. These results suggest that hyperbaric (but not normobaric) oxygen may be useful in the abortive treatment of patients with migraine headache.[76] A total of 14 patients 26 to 56 years old with chronic cluster headaches underwent 15 sessions of treatment with HBO (n=10) or environmental air (placebo) (n=4) provided in a hyperbaric chamber. Compared with environmental air, HBO demonstrated greater clinical efficacy—a finding supported by the appearance of plateaus in the binding curves.[77] In another study,

4 patients underwent a 2-week course of HBO therapy to treat chronic cluster headaches that were unresponsive to pharmacologic treatment. Of these patients, 3 described relief of pain after the treatment period began.[78] In a study of 7 patients with episodic cluster headaches who were given HBO at the onset of an attack, the attack was interrupted in 6 patients. In 3 of those patients, the florid period of the cluster headache was interrupted. The other 3 patients did not experience any painful attacks during a period that lasted 3 to 6 days. In 6 different patients, placebo treatment had no effect.[79]

The effect of HBO on substance P activity in the nasal mucosa has been investigated in patients with cluster headaches. In a study involving such patients, those who underwent HBO therapy demonstrated significantly lower immunoreactivity for substance P than did patients given placebo, indicating that an influence on the peripheral neuropeptides could be involved in the mechanism of action responsible for the beneficial effect of HBO in cluster headaches.[80] The efficacy of HBO in the treatment of patients with migraine and cluster headaches must be further substantiated by prospective, randomized, blinded studies.

Brain Injury

Data from animal and clinical studies suggest that HBO therapy improves healing of the damaged brain. In these studies, HBO inhibited neuronal death and improved neurologic outcomes after cardiac arrest and resuscitation.[81] In animal models, HBO limited the growth of cerebral contusions[82] and appeared to reduce edema produced by moderate fluid percussion.[83] In a review of clinical studies involving patients with traumatic brain injury, some data suggest that HBO therapy may reduce the risk of death after such injury.[84] HBO therapy may also prove to be an important adjunct to surgery and steroid therapy for patients with radiation-induced necrosis within the central nervous system.[85]

The effectiveness of HBO in the treatment of patients with chronic neurologic disorders has been documented.[86] In 320 brain-injured patients, HBO therapy was more efficacious than pharmacologic treatment in resolving clinical symptoms such as hydrocephalus and in controlling epilepsy.[87]

In a prospective randomized trial of severely brain-injured patients at Hennepin County Medical Center in Minneapolis, Minnesota, HBO therapy reduced mortality by 50%. In this study, increased cerebral metabolism of oxygen and decreased cerebral spinal fluid lactate levels after treatment indicated that HBO may improve aerobic metabolism in severely brain-injured patients.[88] In a prospective study of 14 Cuban children with a central nervous system lesion, patients who underwent HBO therapy demonstrated faster and more promising results within the first year after diagnosis than did those who did not receive HBO therapy.[89]

It is interesting to note that in animals with acute compression-dislocation syndrome and cerebral compression caused by edema in the brain, HBO exerts preventive and therapeutic antiedematous actions, minimizing the interhemispheric asymmetry associated with edema.[90] In the traumatized rabbit brain, HBO treatment significantly reduced the amount of tissue water in the brain; a course of 10 sessions proved to be more effective than a course of 6 sessions.[91] In 60 patients who were

comatose from head injury, treatment with HBO reduced the severity of edema and ischemia in the injured zones.[92] In 103 patients with craniocerebral trauma, HBO therapy produced a prophylactic effect on the development of mental disorders during the acute period of brain trauma; it also prevented some related complications, such as meningitis, suppuration of an operative wound, bedsores, and pneumonia. In some patients, however, HBO had no noticeable effect on the rate and strength of recovery of motor and speech functions.[93] In addition, according to a review of the literature pertaining to HBO therapy, reports published before August of 2001 do not support the use of HBO for patients with traumatic brain injury and stroke.[38]

Spinal Cord Injury

Therapy with HBO has been reported to improve neurologic recovery after spinal cord injury and to extend the prime therapeutic period for acute spinal cord injury to 6 hours after injury. In such cases, multiple HBO treatments are more effective than single sessions.[94,95] In an animal model of motor neuron disease, HBO treatment significantly ameliorated mitochondrial dysfunction in the motor cortex and spinal cord and delayed the onset of disease.[96] HBO therapy has also been used successfully to treat patients with type 2 decompression sickness involving the spinal cord.[97] In neural transplantation, a lack of oxygen supply to the graft during the acute stage is a significant problem. Clearly, the reduced edema associated with HBO therapy prevents displacement of the graft from the gap and contributes to the integration between graft and host.[98] The administration of HBO shortly after ischemic insult in rabbits produced protective effects against ischemic spinal cord damage, but delayed treatment with HBO did not change the prognosis.[99]

In a study of sheep that sustained a controlled contusion to the thoracic spinal cord, HBO treatment improved the rate and strength of motor recovery and reduced the severity of cord degeneration—a finding that suggests that ischemia plays a significant role in contusion injury to the spinal cord.[100] In another study of sheep with spinal cord injury, HBO treatment was administered to delay the onset of paraplegia after injury. Results of this preliminary report suggest that early treatment provided within 2 hours of injury can enhance motor recovery.[101]

In a study of patients with various spinal cord injuries (eg, trauma, discogenic ischemic myelopathy, sequelae associated with tumor removal), HBO therapy frequently led to pronounced regression of neurologic symptoms.[102] In these patients, pelvic and motor functions and reflexes returned to normal, and pain syndromes were alleviated. In a retrospective study of patients with acute traumatic cervical spinal cord injury treated with and without HBO therapy in Tokyo Metropolitan Ebara Hospital, Tokyo, Japan, those who received HBO therapy demonstrated a faster rate of recovery than did those who did not.[103] In a study of patients with cervical compression myelopathy who received HBO therapy after surgery, the effect of HBO was more highly correlated with recovery rate after surgery than were other investigated parameters.[104]

Hyperbaric oxygen can serve as a diagnostic tool for evaluating the functional integrity of the spinal cord and for assessing the success of recovery of spinal cord function after surgical decompression. In a study of patients with radiation myelopathy and micturitional symptoms who underwent a combination of steroid pulse therapy and HBO, 2 of 3 patients demonstrated a decrease in micturitional disturbance and other neurologic deficits.[105]

In a rat model, magnetic resonance imaging was used to assess the efficacy of HBO treatment in spinal cord injury.[106] During a treatment period of 72 hours, HBO treatment led to improved neurologic recovery (based on the Tarlov scale) and appeared to arrest the spread of hemorrhage and resolve edema. In lateral amyotrophic sclerosis, HBO therapy produces only a minimal and short-lived positive effect in some patients. In most cases, therapy fails to control or stabilize neurologic disorders. In light of these results, HBO can be recommended as adjunctive therapy in the treatment of patients with vascular damage to the spinal cord.[107]

In 44 patients with chronic osteomyelitis associated with spinal cord injury, HBO therapy administered adjunctively with antibiotic and surgical treatment helped resolve bone infection and promote wound healing.[108] During a follow-up period that lasted between 6 months and 9 years, two thirds of patients demonstrated complete recovery. In another study, 45 patients underwent HBO therapy for a recent spinal cord injury. Among these, 27 with upper motor neuron lesions demonstrated a notable recovery, and 15 patients regained useful functioning.[109]

Hyperbaric oxygen therapy can mediate the preservation of marginally injured neuronal elements of long tracts of the spinal cord during the early phases of traumatic spinal cord injury. This protective effect may be related to the reversal of focal tissue hypoxia or to reduction of tissue edema.[110] Among 13 patients with compressive spinal cord lesions treated with HBO, 6 demonstrated marked improvement, particularly in motor function. The other patients showed only little change in neurologic status. Moreover, arterial and cerebrospinal fluid PO_2 levels measured in 8 patients during the HBO sessions increased considerably during treatment. Increased cerebral spinal fluid PO_2 may be indicative of improved oxygenation of spinal cord tissue during peroxide treatment.[111]

In a study of 25 patients who underwent HBO or conventional therapy for approximately 7.5 hours after acute spinal cord injury,[112] those who received HBO therapy appeared to recover more quickly, although their final motor scores were about the same as those of patients who received conventional therapy. In an animal study in which experimental allergic encephalomyelitis was induced in guinea pigs, those animals that received HBO treatment 5 to 19 days after induction demonstrated clinical signs of the disorder 4 to 6 days later than did animals that did not receive treatment, and they survived 4 to 5 days longer.[113] Results of a 10-patient study show that support of injured spinal cord tissue with oxygen under pressure may improve nerve function without loss of motor power or sensation.[114]

Other Pain Syndromes

Hyperbaric oxygen therapy has demonstrated efficacy in the treatment of patients with pain produced by the decompression sickness that often occurs after diving.[115] Fibromyalgia syndrome is characterized by long-standing multifocal pain with generalized allodynia or hyperalgesia. In a randomized controlled study that evaluated the effect of HBO therapy in treating patients with fibromyalgia syndrome, those who underwent treatment demonstrated significantly less tenderness and pain and a significantly higher pain threshold after the first and fifteenth therapy sessions.[116] In a study of patients with exercise-induced muscle soreness, those given HBO therapy reported faster recovery and less perceived muscle soreness after 3 days of treatment than did those who received no treatment.[117]

In a study by Kiralp et al, 37 of 71 patients with complex regional pain syndrome were randomly assigned to receive HBO and 34 were given normal air (the control group) to relieve wrist pain.[118] Patients given HBO reported significantly less pain and edema and a significantly greater increase in range of motion of the wrist than did those in the control group, but their wrist extension did not improve significantly. These results indicate that HBO is an effective and well-tolerated method of decreasing pain and edema and increasing range of limb motion in patients with complex regional pain syndrome.[118] In another study, 35 patients with complex regional pain syndrome received HBO and an analgesic preparation containing propyphenazone, paracetamol, caffeine, and codeine. After this treatment had been administered, all patients reported significantly less pain and anxiety and fewer autonomic and depressive symptoms.[119]

CONCLUSION

Hyperbaric oxygen therapy is currently in use for the management of many diseases, and its clinical application is expanding. Studies have shown tremendous effects of HBO on nervous system function and disease (Table 3). The clinical benefits of HBO have been demonstrated in patients with stroke, migraine, headache, elevated intracranial pressure, and brain injury. It is clear that previous studies have yielded promising results—strong enough to warrant further clinical study of HBO therapy in patients with nervous system disease, particularly stroke, trauma, infection, atherosclerosis, migraine, spinal cord or peripheral nerve injury, and cerebral palsy. The recommended goal of future studies is to investigate the potential inclusion of HBO as part of standard therapy for patients with nervous system disease.

Table 3. Actions of Hyperbaric Oxygen in Neurologic Disease

Stroke	
	Decreases cerebral edema
	Normalizes water content in the brain
	Decreases brain infarction
	Maintains blood–brain barrier integrity
	Improves outcome
	Increases survival rate
	Induces attenuation of motor deficits
	Prevents complications such as pneumonia, pulmonary edema, and thromboembolism
	Prevents recurrent cerebral circulatory disorders
Atherosclerosis	
	Accelerates regression of atherosclerotic lesions
	Promotes antioxidant defense
	Suppresses proliferation of macrophages and foam cells within lesions
Cerebral palsy	
	Improves function of damaged cells
	Attenuates effects of hypoxia on neonatal brain
	Improves gross motor function and fine motor control; reduces spasticity
Intracranial pressure	
	Causes significant reduction of intracranial pressure
Headache	
	Aborts acute attacks of migraine
	Reduces migraine headache pain
	Prevents cluster headache
Brain injury	
	Inhibits neuronal death
	Improves neurologic outcome
	Alleviates radiation-induced neurologic necrosis
	Promotes blood flow in chronic neurologic disease
	Provides relief from clinical symptoms, controls epilepsy, and resolves hydrocephalus
	Improves aerobic metabolism in brain injury
	Counteracts edema and ischemia
	Prevents complications, such as meningitis, bedsores, pneumonia, and wound infection
Spinal cord injury	
	Improves neurologic recovery
	Ameliorates mitochondrial dysfunction in the motor cortex and spinal cord
	Reduces micturitional disturbance and neurologic deficits
	Arrests spread of hemorrhage, reverses hypoxia, and reduces edema
	Resolves bone infection and helps wound healing in chronic osteomyelitis

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