International Journal of Clinical Medical Research

Hyperbaric oxygen therapy for cerebral palsy

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Volume number 2
Issue number 6
Pages 227-235

10.61466/ijcmr2060005

Received: 02.09.2024
Accepted: 23.11.2024
Published: 25.11.2024
0nline: 01.12.2024

Abstract

Synopsis In a hyperbaric chamber pressurized to more than one atmosphere, 100% oxygen is inhaled as part of hyperbaric oxygen therapy. Several indications for this treatment, such as decompression sickness, carbon monoxide poisoning, serious burns, or chronic infections, have been approved. Based mainly on enhancing oxygen availability to injured brain cells with potential for recovery, especially in the event of a chronic injury, hyperbaric oxygen has been researched in the context of cerebral palsy. There is little data on hyperbaric oxygen in cerebral palsy due to methodological issues, lack of control groups, and precision. The results of three randomized controlled trials show that hyperbaric oxygen does not improve large motor skills compared to controls that used a waiting list or slightly pressurized room air. However, the nature of the power (pressurized room air, for example) and the small number of patients examined make these conclusions debatable. Although bias in their methodology limits observational before-and-after studies, they do raise interest in hyperbaric oxygen for cerebral palsy. Some bad effects of hyperbaric oxygen are middle ear barotrauma, which usually needs a myringotomy and tube insertion and a higher risk of seizures. Hyperbaric oxygen's use in cerebral palsy is still debatable.

Keywords: hyperbaric oxygen; cerebral palsy; hypoxia; postischemic vasoconstriction

Introduction

The evidence of the genuine potential advantages and risks of hyperbaric oxygen treatment is far from certain, despite some research suggesting that it might be useful in the treatment of cerebral palsy. While the outcomes of some of this study have been encouraging, the research to yet has been inconsistent and even inaccurate. The US Food and Drug Administration has approved hyperbaric oxygen therapy for a variety of illnesses and injuries. Box 27.1 is a list of uses that the US Food and Drug Administration currently approves. The list of accepted indications created by the Undersea and Hyperbaric Medical Society in 1978 and updated by them in 2002 and 2014 served as the foundation for the US Food and Drug Administration's approved indications list. [1] Medicare/Medicaid and other insurers typically use the US Food and Drug Administration's approved list for a certain drug or treatment when determining which ones to cover. The US Food and Drug Administration has classed hyperbaric chambers as class II medical devices, meaning that before they can be marketed, their producers must adhere to certain rules. The maker must declare the intended applications of the gadget by the regulatory process. Manufacturers must provide supporting documentation when requesting uses other than the 14 that have already been approved. The Center for Devices and Radiological Health would confer with the Center for Drug Evaluation and Research before reviewing the evidence. Studies involving significant risk would need to apply an investigational new drug, and any trial would need to get permission from the Investigational Review Board. [2] Manufacturers are not allowed to promote or advertise uses that have not received FDA approval. To make matters worse, hyperbaric chambers are now considered prescription devices by the US Food and Drug Administration. For this designation to be used, a current prescription must be obtained. States differ in who can prescribe hyperbaric oxygen to practitioners. A doctor may prescribe hyperbaric oxygen for "off-label" use if they think it's the best course of action for a patient with an indication that

isn't on the list, just like they can with other prescription medications and equipment. While many health systems may fully embrace the use of hyperbaric oxygen therapy for the criteria listed in Box 27.1, the use of hyperbaric oxygen for conditions not on this list—like cerebral palsy—is often not accepted and is therefore not a covered benefit. Information on the cost and costs for hyperbaric oxygen is fairly restricted, but it is reported that in the USA Medicaid pays $400 each session for an inpatient facility, often employing a multi-place chamber. [3] Many patient families have been ready to pay for these services "out of pocket." Although the information on patient fees is hard to come by, monoplane chambers—which are frequently found outside of large medical facilities—are said to offer cheaper start-up and operational costs (USD 48–66 for each treatment session. [4] The length of therapy and the total number of sessions will determine the overall cost.

Hyperbaric Oxygen Therapy: What Is It?

Inhaling 100% oxygen while in a hyperbaric chamber that is pressured to more than one atmosphere (atm) is known as hyperbaric oxygen therapy. Hyperbaric oxygen therapy induces a state of hyperoxia and high pressure, which has both mechanical and physiological effects. Multiples of atmospheric pressure at sea level, or 1 atm, or 760 mmHg, or 1 kilogram of pressure per square centimeter, are used to express hyperbaric oxygen pressure. [5] In addition to hemoglobin-bound oxygen, the amount of oxygen dissolved in blood at 1 atm (sea level) while a person is breathing room air is 0.3 mL/dL. The blood oxygenation increases to 1.5 mL/dL, or almost five times when breathing 100% oxygen at 1 atm. This is in comparison to inhaling regular room air. Blood oxygen (dissolved oxygen, not transported by hemoglobin) rises to 6 ml/dL when pressure is increased to 3 atm. [6] This is a 20-fold increase in blood-borne oxygen, excluding oxygen linked to hemoglobin. Tissues need 5-7 ml/dL of oxygen at rest and with adequate perfusion, whether from dissolved or hemoglobin-bound oxygen. Hence, an increase in dissolved oxygen can meet tissue oxygen needs in conditions where hemoglobin-bound oxygen is limited (such as carbon monoxide poisoning). Boyle's law states that the volume of a gas in an enclosed space is inversely proportional to the pressure applied to it. This reduces the volume of gases in the blood in addition to the hyperoxic effect. This is the method used to treat arterial gas embolism and decompression sickness because it shrinks the gas bubbles and lets oxygen, which can be digested by tissues, replace the inert gas inside. There are two main methods for administering hyperbaric oxygen: a mono-place chamber or a multi-place chamber. [5] The mono-place chamber only serves one patient at a time. Although it is less expensive to set up and run initially, there is less room for patient involvement once the patient is in the chamber. Typically, acrylic view apertures or transparent acrylic are used in the construction of mono-place chambers, which enable patient monitoring. In most cases, 100% oxygen is used to pressurize mono-place chambers. Medical professionals can work in multi-place chambers and provide some acute patient care. The multi-place chamber is inflated with room air, and an endotracheal tube, a tight-fitting hood, or a facemask are used to administer 100% oxygen. Depending on how long they are exposed to the hyperbaric air environment, medical workers may need controlled decompression because the entire multi-place chamber is pressurized with air. Even though a hyperbaric oxygen session lasts between 90 and 120 minutes on average, there is no set length, frequency, or total number of sessions required for treating any permitted or "off-label" application. The patient's dosage may vary depending on the type of chamber utilized. In multi-place chambers, for instance, loosely fitting facemasks or hoods may cause 100% oxygen to be diluted with ambient air. The benefits of hyperbaric oxygen therapy for brain injury are shown in Figure 1. [7]

Why oxygen at hyperbaric pressure?

Local tissue hypoxia increases the risk of infection and impedes the healing process in soft tissue wounds that are chronically infected or non-healing. [5] Hyperbaric oxygen reverses local hypoxia and stops postischemic vasoconstriction. It also helps the production of collagen matrix, which is needed for angiogenesis and getting blood flowing again to the damaged tissue. [5, 6] The application of oxygen deprivation and oxygen therapy to brain injuries is contentious, despite the well-established biochemical and cellular effects of these interventions for soft tissue injuries. The imaging results for the group with severe traumatic brain injury are shown in Figure 2. [8] Current theories of neuronal damage and recovery suggest that a complex series of events culminate in energy failure, mitochondrial dysfunction, oxidative damage to RNA/DNA, and structural or functional brain damage. These events start with the depletion of intracellular ATP and the expression of immediate early genes. [9] This chapter is not intended to provide a comprehensive analysis of the theoretical underpinnings of hyperbaric oxygen therapy for brain injury. The following summary gives a general overview of the ideas of brain pathophysiology and recovery from injury, together with the animal experimental data and human case studies that support these views. A detailed analysis of these hypotheses has been done elsewhere. [10] The discussion that follows outlines some of these ideas' foundations and how they vary from other accounts of brain injury and recovery, although it is by no means exhaustive.

Acute Brain Damage

A stroke happens when an artery that supplies part of the brain is blocked. Anoxic-ischemic encephalopathy happens when shock, low blood pressure, strangulation, or another injury lowers blood flow to the whole brain. In both cases, damage and cell death are unavoidable results of poor blood and oxygen flow.

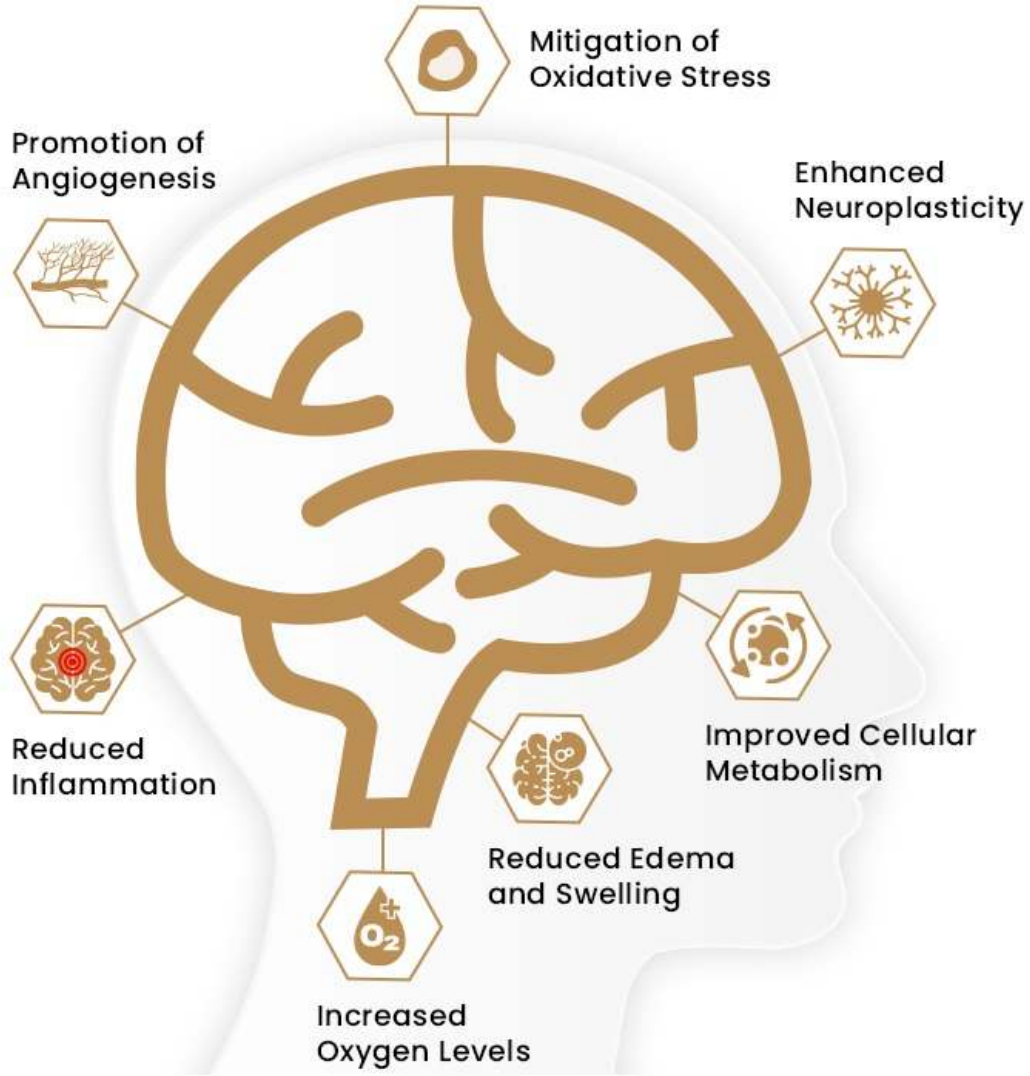

Figure 1. Benefits of hyperbaric oxygen therapy for brain injury.

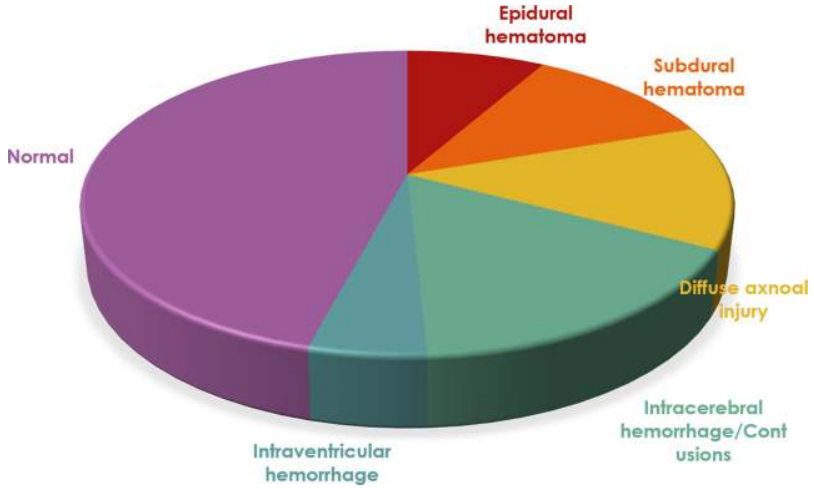

Figure 2. The imaging results for the group with severe traumatic brain injury.

Hypoxia and hypotension are both independently linked to higher rates of death and morbidity in cases of acute traumatic brain injury. Therefore, it is believed that oxygen deprivation and subsequent ischemia are significant causes of cell death in traumatic brain injury. [11] Since brain-injured patients suffer terrible consequences from

hypoxia and hypotension, proactive measures to prevent cerebral hypoperfusion and avoid or correct hypovolemic shock have become cornerstones of trauma care management. However, recent research has cast doubt on these guidelines, claiming that perfusion pressure control has no positive effect on resuscitation outcomes and may even have the opposite effect. Aggressive trauma therapy, however, only slightly lowers the frequency of hypoxic and ischemic episodes—it does not completely eradicate them. This has led to a resurgence of interest in developing more potent methods for supplying sufficient oxygenation and shifting cerebral blood flow to brain damage. Following a brain injury, local injury-related sequelae like ischemia and edema may cause brain cells to become momentarily inactive. These sequelae are believed to impair local perfusion. This outcome supports the use of hyperbaric oxygen therapy, which, as demonstrated by serial single-photon emission computed tomography scans and other techniques, enhances blood flow to the brain's injured regions. [12-14] Hyperbaric oxygen has been shown to inhibit cell death in certain experimental models of acute cerebral ischemia and acute carbon monoxide poisoning, however, the exact mechanism is unknown. [10] Brodmann regions and cognitive functions connected. Improvements in cognitive function were connected with increased perfusion and metabolism in particular Brodmann regions in each of the three groups of traumatic brain injury survivors (mild, moderate, and severe) are shown in Figure 3. [8] The effects of oxygen on the cellular and inflammatory response to damage may be more significant than the redistribution of cerebral blood flow, even if it is a factor. [10] Hyperbaric oxygen, for instance, has been shown to lower brain leukocyte myeloperoxidase activity in a rat model of focal cerebral ischemia. This enzyme is produced by white blood cells called poly-morphonuclear neutrophils and indicates the level of inflammation. When compared to untreated rats, rats randomly assigned to receive hyperbaric oxygen had smaller infarcts and better neurological outcomes; additionally, there was a strong positive correlation between the degree of neurologic impairment and brain leukocyte myeloperoxidase activity. [15] The same researchers observed that dogs treated with hyperbaric oxygen had better neurological results and histologically fewer dead neurons than were dogs treated conventionally in a different model of cardiac arrest and resuscitation. [16] Although it had no bearing on oxygen delivery to the brain or oxygen metabolism rate, the extent of neuronal damage had a strong correlation with neurological consequences. There is not enough evidence to make solid conclusions about the clinical effect in humans. [17-19]

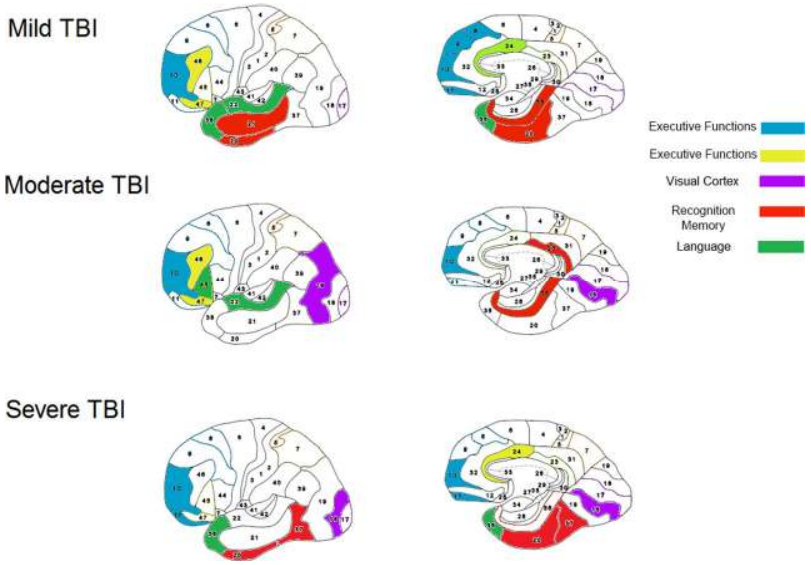

Figure 3. Brodmann regions and cognitive functions connected. Improvements in cognitive function were connected with increased perfusion and metabolism in particular Brodmann regions in each of the three groups of traumatic brain injury survivors (mild, moderate, and severe).

Prolonged Brain Damage

Many people with brain injuries go naturally from a coma to consciousness and back again, sometimes even regaining some cognitive function. This phenomenon of brain injury spontaneous recovery suggests that certain brain cells that have lost function may eventually regain it. This phenomenon of transitory, reversible inactivity of brain tissue is explained by several hypotheses of healing following CNS injury. The idea that there are dormant cells in every brain damage with the possibility of recovery underpins the use of hyperbaric oxygen for stroke, cerebral palsy, and chronic brain injury. These "idling neurons" are thought to be found in the ischemic penumbra, a region of dormant neurons that bridges the gap between portions of healthy tissue that is unaffected by injury and areas of dead tissue. [10, 20] According to the notion, these cells are stimulated to operate normally when oxygen becomes available to them, reactivating them electrically or metabolically. It is helpful to differentiate between this theory and another well-liked neuropsychological hypothesis. According to the neuropsychological view, injury-induced loss of innervation, which originated from cells, renders neurons inactive. [21] This idea suggests that

recovery happens as surviving neurons form new synaptic connections that facilitate the activation of temporally inactive cells. Nevertheless, an independent, critical evaluation of the animal and human evidence supporting this hypothesis and the therapy strategies based on it was recently carried out by the National Institutes of Health Consensus Development Conference. [21] First, the panel saw that there had been no increase in function despite the synaptic rearrangement and "sprouting" shown in the animal brain that had been denervated. Secondly, they pointed out that there is no proof that any treatment, in humans or animal models, genuinely accelerates these physiological processes. There is currently little evidence from either human case studies or animal trials connecting clinically observed improvements in cognitive function to physiological or anatomical measures of synapse enrichment. The amount of treatment, the frequency of family visits, and other forms of stimulation that are thought to encourage the formation of new synaptic connections have been proven to have no association with human research. A limited home rehabilitation program with weekly telephone contact from a psychiatric nurse proved to be just as successful as rigorous in-hospital cognitive therapy for 120 active-duty military soldiers with moderate to severe traumatic brain injury in a randomized trial. [22] The "idling neuron" idea, in contrast to the cognitive stimulation theory, proposes that the restoration of oxygen causes blood vessels to develop and previously dormant neurons to form new synaptic connections. It regards neuron inactivity denervation as the outcome of chronic hypoxia. The hypothesis behind hyperbaric oxygen therapy for brain injury, according to proponents, has a stronger experimental foundation than the theory behind restorative cognitive therapies. [10] Animal models allow for the direct observation of the effects of the suggested treatment—pressurized oxygen—as opposed to the hypothesized effects of cognitive stimulation. The effects of hyperbaric oxygen on physiologic and anatomic endpoints, such as neuronal death, infarct size, and, in certain models, the creation or preservation of synapses, have been studied in animal experiments, as mentioned above. Using serial single-photon emission computed tomography imaging and indicators of cerebral metabolism, the physiological effects of hyperbaric oxygen have also been investigated in human case studies conducted before and following treatment.

Unfavorable effects of oxygen under pressure

Adverse events are associated with elevated pressure and/or elevated oxygen concentration and can happen during compression, therapy, and decompression. While complications like seizures or pulmonary barotrauma can happen and be observed right away, more subdued side effects might manifest themselves after a course of therapy. Concerns about inferior cognitive outcomes in patients receiving hyperbaric oxygen relative to normobaric oxygen are raised by the results of a recent trial on hyperbaric oxygen for acute carbon monoxide poisoning. [23]

Cerebral palsy and hyperbaric oxygen

Five observational before-and-after studies (including 455 patients) and three small randomized controlled trials (with 186 patients) provide the majority of the information about the effects of hyperbaric oxygen on people with cerebral palsy. The Agency for Healthcare Research and Quality in the USA commissioned a systematic review in 2003 to investigate the advantages and disadvantages of using hyperbaric oxygen for the treatment of cerebral palsy and other medical conditions, including severe brain injury. [24] By scientific practice, a systematic review aims to generate a summative assessment of scientific knowledge in a specific field by reviewing all available data from research on a given drug class, disease, technique, or treatment. At that time, no studies specifically examined potential harms associated with hyperbaric oxygen treatment among patients with cerebral palsy, and only six very different research studies had been found that had been specifically designed to determine whether hyperbaric oxygen treatment might offer some benefit to patients and/or their caregivers. Two other studies—a before-and-after study and a randomized controlled trial—have been published after the release of that review. [25, 26] Two related randomized controlled trials give the greatest information to date on the advantages and disadvantages of hyperbaric oxygen therapy in cerebral palsy. [26, 27] The two trials were comparable in that they recruited all or most children with spastic forms of cerebral palsy, with mean ages of 7 years in one and 6 years in the other, and used a sham control group where patients entered the hyperbaric chamber and received slightly pressurized room air. The primary outcome measure was changes in the 88-point Gross Motor Function Measure scale. The minimal clinically significant difference is defined as an increase of more than 2.73 points from baseline. [28] The hyperbaric oxygen regimens varied somewhat; five days a week, for forty sessions, one provided 100% oxygen at 1.5 atm for 80 minutes and the other at 1.75 atm for 60 minutes. In total, 160 kids were involved in both studies. These trials provide moderate-to-strong evidence that pressurized room air or hyperbaric oxygen does not enhance motor skills in children with cerebral palsy. After two months and forty sessions, both groups' motor function ratings in the prior, bigger trial improved in the first research. [27] The children getting hyperbaric oxygen showed an average change in Gross Motor Function Measure of 2.9, while the children receiving simply pressurized room air showed an average change of 3.0. These gains were statistically significant when compared to the baseline, but the group differences were not. The more recent trial's baseline changes (in hyperbaric oxygen and control, 1.5 and 0.6 points, respectively) were negligible and not statistically significant. Two preplanned interim assessments led to the early termination of this trial since it was highly improbable that the results would alter if it continued. Upon combining the findings of these studies by meta-analysis, an absolute score difference of -0.11 (95% confidence interval -1.25 to 1.03, not statistically significant) is discovered. The children were assessed at longer follow-up intervals (6 months in one study, and 3 and 6 months in the other), but no statistically significant changes were discovered between the groups. Secondary outcome measures, such as cognitive tests, did not reveal any difference between the groups in

the Collet et al. [27] experiment. [29] Caretakers of children in the group treated exclusively with pressured room air estimated that their charges had considerably higher mobility and social functioning when measured by the Paediatric Evaluation of Disability Inventory. [27] Comparably, the Paediatric Evaluation of Disability Inventory scale was one of the secondary measures used in the Lacey et al. experiment. [26] Significant differences were observed between the groups when compared to their baseline scores, although statistically significant differences were not observed between them. The Test of Variables of Attention was also performed in this trial, however less than half of the patients were able to finish it, and neither within-group nor between-group differences were seen. We have a moderate degree of confidence that more research won't change the results because of the moderate strength of this evidence. Even though the research findings are usually consistent, there are certain methodological flaws in the studies, and the small sample sizes lead to imprecise estimates. The upper and lower bounds of the confidence interval are smaller than the lowest clinically meaningful difference, which was determined to be 2.73 points. [28] Nevertheless, the pooled estimate for the difference in change in Gross Motor Function Measure scores was statistically significant. Although the design and execution of both of these studies were overall excellent, certain methodological flaws might have introduced bias. Positively, both were correctly randomized and employed validated scales to measure outcomes; however, only Collet et al.'s study employed blinding physical therapists who performed outcome evaluations. [27] There were notable differences between the two groups in the type and presumed cause of cerebral palsy, and at the beginning of the study, there was an average nine-point difference on the Gross Motor Function Measure scale. However, it was unclear in Collet et al. how well the researchers had managed to conceal the order of random assignment from the researchers who were responsible for enrolling patients. [27] This was handled by adjusting the statistical analysis of the change in the Gross Motor Function Measure score to account for the original variation in the score. In the Lacey et al. experiment, there was a 1-year age difference between the groups (6.3 versus 5.2 years) and a 4.2-point difference in baseline Gross Motor Function Measure scale scores. [26] One of the more significant possible drawbacks for both studies could be the lack of clarity regarding the representativeness of the trial participants among children with cerebral palsy. 196 children were checked in Collet et al. [27], of whom 111 were enrolled; similarly, 360 children were screened in Lacey et al., of whom 49 were recruited, even though the 311 children's exclusions were explained. [26] Of these, 89 were determined to be eligible but did not take part; the children's Gross Motor Function Measure results and baseline characteristics were not disclosed. There are five observational studies and one additional randomized controlled trial in addition to these two. The experiment was a pilot study with significant shortcomings and contradictory findings. [30] It involved giving hyperbaric oxygen to two small groups of kids either right away after they signed up for the trial or after a six-month waiting period. The children in both groups were assessed at baseline, one month, two months, and five months by blinded physical therapists and child psychologists using a range of instruments (Bayley II, Preschool Language Scale, Peabody Motor Scales, Paediatric Evaluation of Disability Inventory). No discernible variations between the two groups were observed in any of these evaluations. However, when caretakers used the Paediatric Evaluation of Disability Inventory mobility sub-score to assess the kids, they discovered that the kids who received prompt therapy showed considerable improvement. However, this experiment had numerous scientific faults, one of which is that the caregivers who conducted the assessments may have been prejudiced because they knew which group their kid had been assigned to. [24] The interest in hyperbaric oxygen therapy for cerebral palsy was historically sparked by observational before-and-after research. However, due to inherent bias in study designs and flawed study conduct, these investigations are unable to significantly add to the body of data. The best observational evidence was obtained from a study involving 25 children that assessed fine motor strength using the Jebsen test, tone level using the modified Ashworth scale, and an evaluation of fine motor activities using a videotape. [31] The study also tested gross motor function. The team of researchers that went on to undertake the largest randomized controlled trial (above) also conducted this study, which is frequently referred to as the McGill study. [27, 31] Following hyperbaric oxygen, the Gross Motor Function Measure score improved by an average of 5.3%, according to the study. In terms of gross motor function, the assessment showed that 67% of the children were better after treatment, 29% were better before treatment, and one child in each group was either the same or had not been videotaped after treatment (videotapes were used for assessment, meaning the physical therapists conducting the assessment were unaware of the child's group affiliation). Although the results seem to indicate improvement following hyperbaric oxygen therapy, there were design issues with this experiment that could have affected the outcome. A few days to a month following the treatment could have been the follow-up period, which was not specified. Parental assessments, hand mobility, and tone all improved, but the scales utilized for these evaluations and the percentage of individuals who showed improvement were not disclosed. This study did not stratify the data according to this variation in exposure because it employed distinct techniques at several centers. The results' generalizability was diminished by the exclusion of children on anti-spasticity drugs and a range of aggravating variables, such as recent rhizotomy. However, because (1) consistent baselines were created, (2) outcome assessors were blinded, and (3) validated scales were utilized to evaluate the key end measure, this study is regarded as the highest-quality observational evidence. In a more recent before-and-after trial, two distinct hyperbaric oxygen regimens, a pressured air regimen, and intensive rehabilitation were all combined, and a control group that received only intensive rehabilitation was also studied. When hyperbaric oxygen and compressed air were combined in the trial, the children's improvements in motor function were greater

than those who received only intense rehabilitation. The selection of control subjects, the timing of baseline measurements about treatment initiation, the stability of baseline measurements (i.e., multiple measurements), the lack of blinding of outcome assessors, and the variations in baseline Gross Motor Function Measure-66 scale scores of 0–4.7 points between the groups are among the methodological problems. This study was conducted over ten years, but neither the timing of the two distinct hyperbaric oxygen therapy regimens nor the identification of the control participants during this time were disclosed. Age was taken into account in the analysis, but other baseline patient-level parameters or study-level factors, such as modifications to other facets of the clinical care of children with cerebral palsy during ten years, were not. The remaining observational studies were either extremely low quality due to insufficient information provided to make assessments about the risk of bias or extremely small (seven patients). [32]

Research on the Negative Effects of Hyperbaric Oxygen on Cerebral Palsy

Although ear issues and seizures were recorded, none of the six studies specifically outlined an a priori plan to assess potential risks from hyperbaric oxygen. Children in the hyperbaric oxygen (50% at 1.75 atm) group in the Collet et al. [27] experiment had a substantially higher incidence of middle ear barotrauma than did the control group (27.8% at 1.3 atm; relative risk 1.5, 95% CI 1.1–2.2, p = 0.02). [27, 33] Due to recurrent middle ear barotrauma, one of the 57 children in the hyperbaric oxygen group withdrew from the trial after undergoing 32 of the 40 sessions. In both groups, 58.2% of the children underwent myringotomies and had ear tubes inserted. Regression studies were not able to determine any characteristics that would predict middle ear barotrauma in a follow-up publication, even though gender and the baseline global Gross Motor Function Measure were positively linked with this adverse occurrence. [33] Children with and without barotrauma experienced similar changes in motor function: 3.3 ± 3.9 versus 2.7 ± 3.0 (p = 0.22). Three children (3.6%) in the hyperbaric oxygen group and none in the control group experienced sinus barotrauma. Adverse events were not reported with the same thoroughness or clarity in the second trial. [26] One patient from each group withdrew: one from the pressurized air group withdrew due to a seizure (which the study found was unrelated to the treatment) and one from the hyperbaric oxygen group withdrew due to three episodes of fluid in the nose or ears following treatment and one episode of rectal bleeding that happened at home. The sole adverse event noted was ear pain, and it only occurred in kids who had finished all of their treatments. The incidence of ear pain did not change between the hyperbaric oxygen group and the control group, with 29% (7 of 24) and 36% (8 of 22) respectively (p = 0.755). In one trial, the temporal sequence was not fully recorded, yet 12% of the children had seizures and withdrew. [30] Another observational study excluded children with a history of seizures, however, 8% of children discontinued hyperbaric oxygen treatment for a variety of side effects, including seizures.

Conclusions

The available data is insufficient to determine if hyperbaric oxygen therapy for children with cerebral palsy is significantly better than usual care, or to uncover any potential risks. Although two controlled trials report similar improvements in children who did not receive hyperbaric oxygen, the observational studies reported improvements in subjective measures and in motor function as measured by the Gross Motor Function Measure. This suggests that hyperbaric oxygen may not be the cause of the improvements observed in the observational studies. Uncertainty arises from inadequate methods of assessment, making it difficult to determine the occurrence of adverse events such as seizures and the requirement for ear pressure equalization tubes in children undergoing hyperbaric oxygen therapy. Because bias and confounding are major concerns and these observational studies are of lower quality, evidence from controlled trials is recommended in this case. According to body grades, there is only Grade C evidence to support improvements in several parameters following hyperbaric oxygen therapy, whereas Grade A data indicates that hyperbaric oxygen therapy for cerebral palsy is not any different from pressurized room air. It is unclear how the effectiveness outcomes would change in a population that is more widely defined, but it is also unclear how the risk of side effects would change in a larger, typically sicker group of patients. The dearth of strong evidence on potential risks remains one of the main issues with this body of research to far. Good-quality evidence is necessary for both professionals and patients to consider the advantages and hazards. Regardless of quality, the available research has focused on the advantages while underreporting the negative effects. The definition of ascertainment methodologies was lacking, making it impossible to assess their accuracy and lack of bias. It was also unclear if all severity levels of the adverse events were documented. Crucially, it seems that adverse events are only recorded for trial groups who receive hyperbaric oxygen, and in observational studies, only during and right after hyperbaric oxygen.

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