Austin Journal of Cerebrovascular Disease & Stroke

Open Access

Austin Publishing Group

Review Article

Management of Acute Ischemic Hypoxic Encephalopathy in Newborns with Hyperbaric Oxygen: A Review

Sánchez EC*
Department of Hyperbaric Medicine, Universidad Nacional Autónoma de México, Mexico

***Corresponding author:** E. Cuauhtémoc Sánchez, Department of Hyperbaric Medicine, Hospital Agustín O´Horan and Centro de Especialidades Médicas del Sureste, Universidad Nacional Autónoma de México, Calle 38 # 101c x 27 y 29 Col. Buenavista, Mérida97127, Yucatán, Mexico

Received: September 20, 2016; **Accepted:** November 21, 2016; **Published:** November 23, 2016

Abstract

Objectives: Describe the use of HBO_2 in the management of acute ischemic hypoxic encephalopathy.

Materials and Methods: The therapeutic mechanisms of hyperbaric oxygen in acute ischemic hypoxic encephalopathy are outlined, based on information obtained from peer-reviewed medical literature.

Results: HBO_2 promotes survival of marginal tissue (penumbra), reduces edema, improves microcirculation, breaks the edema-hypoxia-edema vicious cycle, enhances healing, promotes growth factors up-regulation and improves neovascularization. At cellular level, it maintains the levels of ATP, restores mitochondrial dysfunction, reduces oxidative stress and apoptosis, and promotes anti-oxidant effects. HBO_2 did not show significant differences in fatality rates at six months (RR0.97, 95%CI 0.34 to 2.75, p=0.96). It showed improvement in the disability and functional performance scales. Trouillas Disability Scale was lower with HBO_2 (MD 2.2 point reduction with 95%CI 0.15 to 4.3, p=0.04), and the mean Orgogozo Scale was higher (MD 27.9 points, 95%CI 4.0 to 51.8, p=0.02).

Conclusion: When used promptly, HBO_2 can modify cerebral inflammation, ischemia, hypoxia, and ischemia-reperfusion injury. It helps preserve marginal tissue and recover the ischemic and metabolic penumbra. A prospective, randomized, and controlled study within the window of opportunity (< 5h) in a stroke center is needed, to determine the real use of HBO_2 in these cases.

Keywords: Acute ischemic hypoxic encephalopathy, Hyperbaric oxygenation, Ischemia-reperfusion-injury, Mitochondrial dysfunction

Introduction

Acute ischemic-hypoxic encephalopathy (stroke) is the most important preventable cause of disability for Americans and the second cause of death worldwide. Every year, more than 795,000 people in the US have a stroke and about 610,000 of these, are first or new strokes. About 25% of strokes (185,000) happen in people who had a previous stroke. The prevalence of stroke (2009-2012) for people aged 20-39, was 0.2 for men and 0.7 for women; for ages 40-59, 1.9 for men and 2.2 for women; for ages 60-79, 6.1 for men and 5.2 for women; and for ages 80+, 15.8 for men and 14.0 for women. About 87% of all strokes are ischemic strokes [1-3].

The risk of having a stroke varies with race and ethnicity. The risk of having a first stroke is nearly twice as high for African Americans compared to whites, and African Americans are more likely to die following a stroke than are whites. Hispanics' risk of stroke falls between that of whites and African Americans. American Indians, Alaska Natives, and African Americans are more likely to have had a stroke than all other groups [1-3].

The incidence of mortality and morbidity due to neonatal acute ischemic-hypoxic encephalopathy (AIHE) has not changed substantially in the last 40 years. It is estimated that close to 25% of the neonatal deaths and 8% of all deaths at 5 years of age throughout the world, annually, are associated with signs of asphyxia at birth [4,5]. Death or moderate to severe disability can occur in 50-60% of infants diagnosed as having moderate to severe AIHE [6,7].

The average length of stay in non-federal short-stay hospitals was 4.8 days, although in some hospitals; it extended to up to 10.9 days [3]. The annual cost of stroke in the US is estimated in $34 billion. It includes the cost of health care services, medications and workdays lost [1-3]. Stroke has high direct costs and very high indirect costs. It is estimated that indirect costs account for 80% of the total cost. According to the World Health Organization (WHO) stroke will become the fourth cause of the Global Burden of Disease (GBD) in 2030 [8,9].

In some clinical studies, the 5-year survival rate is 50%. Specialized stroke units have reduced morbidity and mortality (OR 2.2, 95%CI 1.6-2.8, p<0.001), but less than 20% of all stroke cases arrive at the units within the window of treatment (3 to 5 hours) [10]. The phrase "time is brain", emphasizes that human tissue is rapidly lost as stroke progresses and emergent evaluation and therapy are required [11].

AIHE is such a devastating pathology that any gain, no matter how small, can make a big difference in these children's and their families' quality of life (QoL). Prompt treatment should restore adequate perfusion and correct metabolic or cellular alterations. Maintaining adequate perfusion and the cellular metabolic needs may be the cornerstone to reduce CNS damage and promote early

Citation: Sánchez EC. Management of Acute Ischemic Hypoxic Encephalopathy in Newborns with Hyperbaric Oxygen: A Review. Austin J Cerebrovasc Dis & Stroke. 2016; 3(2): 1049.

neuro protection [3,12,13]. The extent of the damage depends on the duration, extension, localization, comorbidities and metabolic changes of the lesion [3,14].

Pathophysiology of AHIE (Ischemia-Reperfusion Injury)

When there is an interruption of the cerebral blood flow or oxygen supply to the Central Nervous System (CNS), several changes occur depending on the degree of hypoxia; these could be reversible or irreversible [15]. Reversibility depends on the mitochondrial ability to maintain ATP production. Once it stops, there is a dysfunction of the ion pumps (Na-K and K-Ca) that eventually will create cytotoxic edema. When the mitochondrial dysfunction is severe, calcium is released into the cytoplasm and becomes the first inflammatory mediator [16,17].

The main player in the pathophysiology of acute ischemic-hypoxic encephalopathy (AIHE) is the ischemia-reperfusion injury (IRI) to the Central Nervous System (CNS). The injury is the result of a series of ischemic and metabolic events that present shortly after the interruption of flow, oxygen, and nutrients to the affected regions of the brain [3].

The center of the lesion is the area of necrosis surrounded by the area of ischemia, hypoxia, and edema, i.e. the recoverable area of the brain (penumbra). The area of penumbra constitutes close to 80% of the damaged brain in IRI. If the ischemic and metabolic penumbras are not resolved in a timely and effective fashion, the damage will extend and deepen due to IRI and apoptosis [3].

Mitochondria in AIHE: There are seven stages of cellular shock in (AIHE). The first four stages are reversible. The reversibility depends on cells' capability to maintain adenosine tri-phosphate (ATP) production by the mitochondria [8]. Once ATP is reduced beyond a critical level (< 1 mol/kg), there is an energy crisis within the cell [9]. During the CNS energy crisis, hypoxia upsets the passage of protons (H+) across the mitochondrial complexes, reducing production of ATP at the ATPase-synthase level. This produces oxidative stress and the increase of reactive oxygen species (ROS)and its production inside the mitochondria; also, the promotion of neural (nNOS) and inducible nitric oxide synthase (iNOS) production [18,19]. If the oxidative stress is not controlled early, it will progress to oxidative damage. This generates an increase of the intrinsic apoptotic pathway. The energy crisis also promotes glutamate production, the most important excitatory transmitter in the brain [20-22].

With mitochondrial dysfunction, there is a loss of calcium-potassium and sodium-potassium cellular pumps, which creates ionic misbalance and cytotoxic edema. The release of cytochrome C occurs immediately before total mitochondrial dysfunction, due to the rise of nitric oxide. The opening of the mitochondrial transition pore follows. Once the pore is open, it releases its calcium content into the cytosol, increasing cellular edema and affecting cellular homeostasis [3,23-26].

Inflammation in AIHE: Calcium is the first modulator of inflammatory cascades [27,28]. It stimulates the activation of calcium protease, which enhances xanthine dehydrogenase conversion to xanthine oxidase, promoting the production of reactive oxygen species (ROS) [29]. It also stimulates the arachidonic acid cascade with the subsequent elevation in the levels of cyclooxygenase (COX), lipoxygenase, leukotriene, thromboxane and prostaglandins [30]. It also promotes the expression of the most important transcription factor for inflammation, nuclear transition factor kappa b (NFκb) and enhances the production of endothelins and cytokines (IL-1, IL-6, IL-8, TNF-α) [31-34]. There is also an elevation of interferon-Y, glutamate, Caspases (3,8, and 9), hypoxia induced factor-1α (HIF-1α), and nitric oxide from inducible nitric oxide synthase (iNOS) [35-38].

At endothelial level, there is an increased expression of adhesion molecules (selectins, vascular adhesion molecule, intercellular adhesion molecule) and leukocyte (integrin beta 2).In the late phase of IRI, the adhesion molecules are the predominant mediators of damage, promoting leukocytes production of ROS, perivenular arteriolar vasoconstriction, apoptosis, and creating the no-flow state [39-42].

Few of the early neuro protectors tested have made a real difference. Stenting, angioplasty, hypothermia, and thrombolysis have shown benefits, especially when applied in the first 3 to 5 hours of the onset of AHIE. Only the Food and Drug Administration (FDA) has accepted the plasminogen activator (rtPA) [43-48]. Nevertheless, none of these have proven to resolve the metabolic penumbra. Medication has not shown the same neuroprotective effects of other therapies [49-51].

Growing evidence suggests that a spectrum of epigenetic processes play an important role in the pathophysiology of cerebral ischemia. DNA methylation, histone deacetylase, histone methylation and micro RNAs (miRNAs) regulate vascular and neuronal regeneration after cerebral ischemia. MiRNAs are supposed to be potential biomarkers for stroke and other related pathologies. Epigenetic strategies for ischemic stroke treatments may modulate neural cell regeneration and promote brain repair and functional recovery [52,53].

Hyperbaric Oxygen in Acute Hypoxic Ischemic Encephalopathies

Hyperbaric oxygen (HBO_2) is a treatment option in which a patient breathes 100% oxygen while inside a treatment chamber at a pressure higher than 1.4 atmospheres absolute (atm abs). The treatment chamber could be mono- or multi place [3,54].

HBO_2 is based on gas laws. Increasing the pressure inside the chamber will promote the amount of oxygen that will dissolve in all body fluids, especially in plasma. The normal treatment pressure varies from 1.5 to 3.0 atm abs and lasts from 45 to 120 minutes, except for diving accident management that could take longer. The primary effect of breathing oxygen at pressure is hyper oxygenation. Partial pressures in plasma at 2.0 atm abs are close to 1500 millimeters of mercury (mmHg) and at 3.0 atm abs are around 2200 mm Hg [3,54].

HBO_2 produces several secondary effects. Hyper oxygenation increases the endovascular oxygen partial pressure. Restoring tissue oxygen tension to normal or supernormal levels, will break the edema-hypoxia-edema vicious cycle. The vasoconstriction effect of HBO_2, without affecting tissue oxygenation due to the increased partial pressure of oxygen, reduces tissue edema and

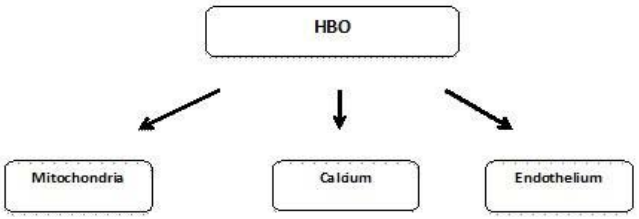

Figure 1: Effects of hyperbaric oxygen on IHE (part 1).
Restores O2 levels Chelates calcium from cytosol <Expression of Maintains ATP levels Stabilizes Na/K ATPase ICAM-1 <Intrinsic ROS production Stabilizes Ca-dependent enzymes Integrin β2> Bcl-2 < IRI < Damage <Bax <Production of glutamate <Endothelins <Caspases 3 and 9 <Cytotoxic edema <Aquaporin < Apoptosis damage.

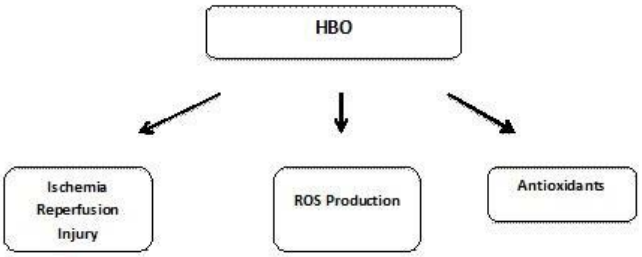

Figure 2: Effects of hyperbaric oxygen on IHE (part 2).
< XO expression (< ROS) <Mitochondrial production > SOD <nNOS and iNOS <XO production > Catalase < Phospholipase A2 <Phospholipase production > GSH-P Lipoxygenase <nNOS and iNOS production > HO-1 Cyclooxygenase > Nrf-2 Modifies NFKb expression > Glutathione < IL-1, IL-6, IL-8> HSP < TNF-α, IFN-Y > IL-10 Modifies Nogo-A/ Rho-A > HSP Modifies miRNA Modifies MMP Modifies HIF-1α.

improves microcirculation [55,56]. HBO_2 also restores damage to the blood brain barrier (BBB) [57,58] and modulates the aquaporin 1response in the choroid plexus, neurons; and astrocytes; aquaporin 4 in astrocytes; and aquaporin 9 in astrocytes and catecholaminergic neurons [59,60].

HBO_2 promotes wound healing, angiogenesis, lymphogenesis, and increases growth factor production [3,12,54,55,61-67]. HBO_2 has direct and indirect antimicrobial effects [12,68,69]. It promotes bone remodeling [70-72] and has rheological effects that are synergistic with pentoxifylline [73]. It also reduces hyper coagulation induced by zymosan and in multiple organ failure [74,75]. Finally HBO_2 increases the mobilization of stem cells from bone marrow and has been used for traumatic brain injury and spinal cord injury [76-78].

By reducing cerebral loss of energy, hyperbaric oxygenation restores cellular ion homeostasis, reduces acidosis, and stabilizes cellular calcium. It also limits excitatory mediators, ROS toxicity, apoptosis, and ischemia reperfusion injury. This is accomplished through several mechanisms. First, it increases oxygen tension and restores oxygen content at tissue and cellular level. If it is applied in a timely fashion, it salvages the cerebral ischemic and metabolic penumbrae, and restores mitochondrial oxidative phosphorylation (Figure 1) [3,12,79,80].

The restoration of cellular oxygen tension and mitochondrial function reduces the expression of NFkB, phospholipase A_2, release of calcium, production of COX-2 miRNA, cytokines (IL-1, IL-6, IL-8, and TNFα), iNOS, and nNOS. Paradoxically, it increases the level of IL-10, an anti-inflammatory cytokine, also mediated by NFkB [3,12,81-85].

Hyperbaric oxygen restores the flux of protons (H^+) in the mitochondrial complexes, thereby restoring the production of ATP. This limits mitochondrial DNA (mtDNA) damage, Caspases expression, oxidative damage (by ROS), the expression of the Nogo-A, Ng-R, and RhoA transcription factors; and it has an anti-apoptotic effect by increasing BCL-2, heme oxygenase-1 (HO-1), and heat shock proteins (HSP-70 and 72) [86-89].

Hyperbaric oxygen reduces the expression of intercellular adhesion molecule-1 (ICAM-1) and endothelin-1, at the endothelium, and neutrophils β2 integrin; with the concomitant reduction of the late phase of ischemic reperfusion injury (IRI) [90-93]. In addition to HBO_2 protective effects through the restoration and maintenance of oxygenation, it also provides antioxidant protection by inducing selective gene and chaperone production [94-96]. The antioxidant effects are also provided by the increased enzymatic (superoxide dismutase, glutathione peroxidase, Nrf2 and catalase) and non-enzymatic (glutathione and cysteine) antioxidant protection (Figure 2) [97-99].

Hyperbaric oxygen has been used for acute hypoxic ischemia encephalopathies (cerebral ischemia and stroke) for more than forty years. Despite the quality and number of articles published, they have not been able to produce enough sound evidence to place HBO_2 as an accepted adjunct treatment option for acute stroke [3].

There are reports involving more than 2000 cases and series of cases. A 2014 Cochrane review by Bennett, et al included eleven randomized, controlled studies involving 705 participants. No significant differences were noted in the case fatality rate at six months in the HBO_2 group compared to the control group (RR 0.97, 95%CI 0.34 to 2.75, p=0.96). Four of 14 scale measures of disability and functional performance indicated improvement following HBO_2; the Trouillas Disability Scale was lower with HBO_2 (MD 2.2 point reduction with 95%CI 0.15 to 4.3, p=0.04), and the mean Orgogozo Scale was higher (MD 27.9 points, 95% CI 4.0 to 51.8, p=0.02). They concluded that further research is required to better define the role of HBO_2 in acute stroke [100].

Use of Hyperbaric Oxygenation (HBO_2) in AHIE in Neonates

HBO_2 use in neonates was almost completely discontinued after Hutchinson's and the USSR experiences. Presently, the largest experience was published by China. The justification for the use of HBO_2 in neonates was the minor modification in morbidity and mortality rates in the last four decades, and the increasing published experience of its possible effects as an early neuro protector. The major controversy was the possible side effects of HBO_2, especially neonatal retinopathy [101].

It is recommended that neonates treated with HBO_2 should be older than 34.5 weeks of gestation, and weight above 1.2 kg. Younger neonates with a lower weight, have a higher possibility of developing complications due to prematurity itself. The most important one would be a pulmonary complication, and retinopathy [102,103]. In the USSR they only treated term neonates reducing the possibility of HBO_2 side effects related to prematurity.

Normally, AHIE is more frequent in neonates with Apgar scores below 3 at one minute and below 5 at five minutes of life, when the resuscitation efforts last longer than 8 minutes, and when the pH is lower than 7.2. Neonates presenting such conditions will require management in a neonatal intensive care unit (NICU). Normally they will present cerebral edema at 4 hours and seizures at 6 hours, thus aggravating their already critical cerebral condition [104-106].

The evaluation of neonates with HIE should include: electroencephalogram (EEG), visual and auditory evoked potentials (EP), transfontanellar Doppler imaging, fundoscopic evaluation, and laboratory tests. The test should be repeated 4 hours after the first HBO_2 treatment and after 24 hours. The HBO_2 treatment should start as early as possible, the sooner the better. It should be within the first 6 hours to guarantee better results. Nevertheless, if there is a good coordination between the neonatologist and the hyperbaric oxygen department, the treatment can start once the patient has been stabilized (first hour). The standard of care inside the hyperbaric chamber requires an inside attendant (neonatologist) and should be the same as in the NICU [101].

There are several special considerations for the treatment of a neonate patient inside a hyperbaric chamber. One of the main problems Hutchinson encountered was the lack of appropriate neonatal medical equipment for hyperbaric use. This has not changed in the last 40 years. There is no neonatal hyperbaric ventilator, although there is a manufacturer that has a hyperbaric ventilator and a neonatal one, but does not see a market for a neonatal hyperbaric ventilator. Also, there are no hyperbaric IV pumps available that can deliver the reduced flows needed by neonatal patients (½ ml per hour) [101,107,108].

To cope with these technical deficiencies, a trained neonatologist should go inside the hyperbaric chamber and ventilate the patient with an Ambu bag. To deal with the low IV volumes required we had to turn the IV pump on and off to be able to deliver the required IV flow. The patient was monitored with ECG and with a transcutaneous oxygen monitor (TCOM). TCOM is used routinely for our ICU patients treated inside the hyperbaric chamber, because it is very sensitive for changes in patients' ventilation. A Bispectral index monitor (BIS) can be used to monitor frontal EEG during HBO_2treatment; it also helps in evaluating patients' sedation and can be a useful tool to detect early abnormal EEG activity related to oxygen toxicity to the CNS [101].

A transfer protocol in coordination with the NICU and the Hyperbaric Unit should be developed to refer the patient as soon as possible (<4 h). The treatment profile is 1.8-2.0 atmospheres absolute for 45 minutes (20 minutes oxygen, 5 minutes air brake, 20 minutes oxygen), QD or BID. The air brake was included to reduce the pulmonary oxygen toxicity of HBO_2. To avoid hypothermia, the chamber linen was warmed to 40°C in water vapor. The recommended pressurizing and depressurizing rate was 1 psi per minute. Myringotomies should be performed before starting the treatment. The patient should be monitored during the entire procedure. Normally, the patients will be ventilated and dependent on cardiotonic medication. The range of delay to treatment after resuscitation should be less than 4 hours. [101].

Acute hypoxic ischemic encephalopathy in neonates is a devastating lesion, its morbidity and mortality has not been modified significantly in the last forty years [109-111]. Any beneficial effects in salvaged tissue will make a big difference in the quality of life of patients, their families and society. HBO_2 has shown beneficial effects on IRI, including the CNS [112-118]. It could be an effective treatment for neonatal AHIE

HBO has been used in neonatal rats for hypoxic ischemic brain damage (HIBD) [119,120], and for necrotizing enterocolitis (NEC) [121]. In the model of unilateral carotid artery ligation followed by a 2.5 hours hypoxia (8% O_2 at 37°C) in 7 days old rat pups, Calvert, et al. showed a reduction in atrophy and apoptosis in the HBO treated animals. The sensorimotor function was also improved by HBO ($p<0.05$) [119]. Wang et al., observed that HBO promoted cell proliferation of neural stem cells, improving some of the neurologic performances, and alleviating the brain damage ($p<0.05$). The therapeutic window for effective HBO treatment could be delayed up to 12 h after HBO, while the effect decreased 24 h after HIBD [120]. Guven, et al. reported that HBO had an ameliorating effect on oxidative stress, nitrosamine stress, and antioxidant enzymes activities in the intestine of pups subjected to NEC [121].

Hyperbaric Oxygen Side Effects

Pediatric patients are no different than adults, nevertheless neonates are. The fear of oxygen toxicity in neonates has hindered its use in them. In general, term neonates have a good anti-oxidant defense; but premature babies and with low weight, may be at risk due to their immature antioxidant defense system. Although neonatologists are very concerned about premature retinopathy, several publications refer to it as an IRI (it occurs after long exposures to oxygen at FiO_2 of 0.45 or higher, and only after oxygen is discontinued). HBO_2 seems to protect them, instead of causing side effects [101,122-125].

Special care should be taken during treatment to avoid hypothermia and oxygen toxicity, especially pulmonary, in neonates with risk factors for bronchopulmonary dysplasia and/or hyaline membrane. Pulmonary surfactant should be readily available in the event the patient presents pulmonary oxygen toxicity. CNS oxygen toxicity is also a possibility that should be taken into account when treating neonates. The use of bi spectral index monitoring (BIS) could show early signs of it and could be promptly and adequately treated. No other types of hyperbaric oxygen toxicity have been reported in neonates so far [101].

Hypothermia

Lately there have been several reports on hypothermia and its beneficial effects [112]. In a meta-analysis on cooling newborns with hypoxic ischaemic encephalopathy published in 2013, it was reported that in 11 randomized controlled trials comprising 1505 term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia; therapeutic hypothermia resulted in a statistically significant and clinical reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (RR 0.75 [95% CI 0.68 to 0.83, NNT – 7 (95% CI 5 to 10]). Cooling also resulted in statically significant reductions in mortality (RR 0.75 [95% CI 0.64 to 0.88, NNT – 11 (95% CI 5 to 14]).

Some adverse effects of hypothermia included and increase sinus bradycardia, increased blood pressure, increase oxygen requirements, and a significant increase in thrombocytopenia. They were transient and reversible after rewarming [126].

Hypothermia may modify apoptosis, reduces cerebral metabolic rate, attenuate the release of excitatory amino acids (glutamate, dopamine), ameliorating the ischemia-impaired uptake of glutamate and lowering production of nitric oxide and free radicals. Some aspects of cooling therapy that remain controversial include: adequate selection of infants, how soon after the insult or birth does cooling need to be started, what level of hypothermia is required, what method (selective head cooling versus whole body cooling) should be used, and what is the duration of cooling required. Time is another critical factor in instituting hypothermia therapy for the newborns. The referral to experienced centers might take away the therapeutic window (< 6 h) .

It appears that HBO and hypothermia might have a synergistic effect if they were combined. There is only one report that deals with both therapies used for a patient with hydrogen sulfide intoxication [127-130]. HBO was used before cooling, not simultaneously. Further research is needed in this area to determine the beneficial effects when both therapies are used simultaneously.

Conclusion

In order to define the role of hyperbaric oxygen in the management of acute stroke there is a need to establish a national and international task force to standardize a treatment protocol to be used with the gold standard treatment, in a timely fashion (< 5h), to clarify its real benefit in the management of AHIE.

The timely restoration of cerebral flow in the acute stroke will resolve the ischemic penumbra but does not deal with the metabolic penumbra. To adequately resolve this, it is mandatory to use a treatment option that can restore cellular and tissue oxygen tensions. HBO_2 has proven to be beneficial in the ischemia-reperfusion injury to other parts of the body. There is increasing evidence on the beneficial effects of hyperbaric oxygen in AHIE [124]. Nevertheless, hyperbaric physicians need to produce evidence following the accepted clinical guidelines of the "gold standard treatment" during the same window of opportunity. This can only be accomplished when there are critical care hyperbaric chambers inside the stroke units.

HBO_2 appears to be a safe and very cost-effective treatment for the AHIE of the neonate [125]. It promotes survival of marginal tissue (penumbra), reduces cerebral edema, restores mitochondrial dysfunction, breaks the edema-hypoxia-edema vicious cycle, and improves microcirculation. It also enhances healing, promotes up-regulation of growth factors and reduces, inhibits or prevents IRI. It reduces iNOS-mediated sepsis and shock. Beside the beneficial effects caused by cellular and tissue oxygenation, it has also a very important antioxidant and anti-apoptotic effect [101]. HBO_2 significantly reduces neurologic sequelae and mortality [125].

If we can overcome the fear of treating neonates inside a hyperbaric chamber, develop better and adequate equipment for the management of these patients during HBO_2, and produce a multicenter, multinational, prospective, randomized, and controlled study; hyperbaric oxygenation will undoubtedly show its beneficial effects in acute hypoxic ischemic encephalopathy of the newborn. This would dramatically change newborn morbidity and mortality and could reduce the global burden of this disease and become a very cost-effective treatment.

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Austin J Cerebrovasc Dis & Stroke - Volume 3 Issue 2 - 2016
ISSN : 2381-9103 | www.austinpublishinggroup.com

Citation: Sánchez EC. Management of Acute Ischemic Hypoxic Encephalopathy in Newborns with Hyperbaric Oxygen: A Review. Austin J Cerebrovasc Dis & Stroke. 2016; 3(2): 1049.