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Ivan David Lozada-Martínez,
Oscar Javier Diaz-Castillo,
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Jhon Jairo González-Monterroza,
Teddy Javier Padilla-Durán,
H. Sebastián Castillo-Pastuzan,
Jhoan Sebastián Robledo-Arias,
Maria Paz Bolaño-Romero,
Alfonso Pacheco-Hernández,
Luis Rafael Moscote-Salazar

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Ivan David Lozada-Martínez[1,2,3,4], Oscar Javier Diaz-Castillo[5], Michael Gregorio Ortega-Sierra[6], Jhon Jairo González-Monterroza[7], Teddy Javier Padilla-Durán[7], Harold Sebastián Castillo-Pastuzan[8], Jhoan Sebastián Robledo-Arias[9], Maria Paz Bolaño-Romero[1], Alfonso Pacheco-Hernández[1,2,3], Luis Rafael Moscote-Salazar[1,2,3]

[1] Medical and Surgical Research Centre, Cartagena, COLOMBIA
[2] Colombian Clinical Research Group in Neurocritical Care, University of Cartagena, Cartagena, COLOMBIA
[3] Latin American Council of Neurocritical Care, Cartagena, COLOMBIA
[4] Globan Neurosurgery Committee, World Federation of Neurosurgical Societies
[5] Medical and Surgical Research Centre, Universidad del Sinú, Cartagena, COLOMBIA
[6] School of Medicine, Corporación Universitaria Rafael Nuñez, Cartagena, COLOMBIA
[7] School of Medicine, Universidad del Magdalena, Santa Marta, COLOMBIA
[8] School of Medicine, Universidad de Nariño, Pasto, COLOMBIA
[9] School of Medicine, Universidad del Quindío, Armenia, COLOMBIA

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Corresponding author:
Ivan David Lozada-Martínez

Medical and Surgical Research Centre, Cartagena, Colombia

ilozadam@unicartagena.edu.co

ABSTRACT

The extent and progression of neurological impairment in traumatic brain injury depend significantly on the area of perilesional gloom, where neuronal apoptosis occurs. Inhibition of apoptosis becomes a therapeutic strategy to preserve brain tissue and promote functional recovery. Hyperbaric oxygen therapy is a treatment by which 100% oxygen is administered, with the aim of achieving a higher pressure than atmospheric pressure at sea level, to decrease ischemia and intensity of inflammatory processes triggered, compromising the viability of the tissues. For mild traumatic brain injury, studies indicate that hyperbaric oxygen therapy is no better than sham treatment. For acute treatment of moderate to severe traumatic brain injury, although the methodology is questionable in certain studies due to the complexity of the brain injury, hyperbaric oxygen therapy has been shown to be beneficial as a relatively safe adjunctive therapy. The objective of this review is to discuss aspects related to the pathophysiology of traumatic brain injury, the mechanism of action of hyperbaric oxygen therapy, and correlate these results with the use of this therapy in the prevention of neuronal injury, supported by original studies reported in the scientific literature

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Introduction

Traumatic Brain Injury (TBI) is generated when there is a sudden acceleration-deceleration process inside the skull caused by all kinds of external forces, among which traffic accident is one of the most common causes [1]. It is considered a major global health problem, being one of the main causes of death and disability, entailing functional, social and economic consequences [2,3] Brain injury in cranial trauma is triggered in two stages, the first occurs immediately after the initial mechanical impact, and in most patients is terminated before admission to the medical institution, representing a permanent neuronal loss [1,4]. Subsequently, within hours, days, and sometimes even weeks, given the insufficient oxygen supply of the surrounding regions, biochemical and metabolic processes are generated that culminate in the apoptosis of neuronal cells [4].

Considering the fact that energy metabolism in the brain is based on aerobic processes, Hyperbaric Oxygen Therapy (HBOT) has been proposed in recent years as a neuroprotective strategy directed towards the containment of secondary processes, in addition to the preservation and reactivation of the penumbra area [5,6]. The objective of this review is to discuss aspects related to the pathophysiology of traumatic brain injury, the mechanism of action of hyperbaric oxygen therapy, and correlate these results with the use of this therapy in the prevention of neuronal injury, supported by original studies reported in the scientific literature.

How hyperbaric oxygen therapy works?

HBOT targets TBI-induced ischemia by exposing patients to an environment that exponentially increases the amount of O2 inspiration, producing hyperoxia in the plasma, and consequently, an accentuation of O2 supply for diffusion to brain tissue, where hypoxia can be decreased, and thus, prevent neuronal death [7,8]. For mild TBI, studies indicate that HBOT is no better than sham treatment [9]. For acute treatment of moderate to severe TBI, although the methodology is questionable in certain studies due to the complexity of the brain injury, HBOT has been shown to be beneficial as a relatively safe adjunctive therapy [7,9].

The therapeutic effects in moderate TBI, are attributed to several pathophysiological mechanisms, including: increased arterial oxygen pressure and oxygen levels in brain tissue, increased diffusion velocity and effective oxygen diffusion distance, reduction of brain tissue edema and intracranial pressure, neuronal protection from ischemic death by acceleration of collateral circulation, stimulation of angiogenesis and neurogenesis accompanied by repair of injured microcirculation, and prevention of microthrombus formation [7,8,10]. Other studies have shown that repetitive application of HBOT after moderate TBI attenuates reactive astrogliosis and glial scarring, in addition to decreasing the expression of inflammatory mediators [11]. Additionally, research in murine models with moderate TBI induced and treated with HBOT showed improvement in spatial learning and memory [7,12].

During the acute phase of severe TBI, the metabolic demands of the brain increase, but O2 delivery to the brain is limited due to a reduction in cerebral blood flow, as well as diffusion barriers caused by capillary endothelial edema [7,8,13]. This O2 deficiency causes failures in cellular respiration and other aerobic biochemical events, activating the anaerobic machinery, with consequent depletion of cellular energy (ATP), and finally, cell death [8]. The crisis resulting from inadequate O2 supply produces electrolyte imbalance, secondary to the lack of energy for the normal function of the Na+/K+ ATPase pump within the cells of the nervous system [8,14,15]. This imbalance leads to increased calcium influx, resulting in considerable release of excitatory neurotransmitters, and further disruption of mitochondrial metabolism, resulting in excessive accumulation of free radicals and as the neuroinflammatory response continues, apoptosis-mediated proteins initiate the process of cell death [8,16].

Mechanism of neuroprotection

Most of the damage following TBI occurs due to a secondary process. This includes cell death, oxidative stress, neuroinflammation and glutamate excitotoxicity [14,15,17]. Baratz-Goldstein et al [7]. showed how immediate and delayed HBOT, can ameliorate the elevation of reactive astrocytes seen after moderate TBI, successfully preventing the demyelination process [7]. In addition, it has been reported that following TBI, there is a decrease in previously elevated inflammatory processes, such as inhibition of caspase 3, TNF-α expression, NF-κB,

upregulated microglia, and elevation of IL-10 [13,18,19]. Based on the above, it can be said that HBOT exhibits multiple mechanisms of neuroprotection (Table 1). Considering the above, when additional O2 is available for diffusion through the capillary endothelium, anaerobic metabolism is converted back to aerobic metabolism, allowing mitochondria to restore depleted cellular energy [8,16].

The upregulation of Nrf2 was suggested as one of the mechanisms that help protect neuronal loss [18]. Yang et al [19]. evaluated HBOT treatment following intracerebral hemorrhage in murine models, finding that this intervention upregulated microglia characteristics, potentially decreasing diminished neuronal loss [19].

Another explanation for the neuroprotective qualities of HBOT in moderate TBI is related to changes in cerebral blood flow [7,8]. HBOT stimulates vasoconstriction, leading to a decrease in cerebral blood flow. This mechanism promotes neuroprotection as it reduces trauma-induced intracranial pressure and cerebral edema, thus improving cognitive functions [8,16]. This effect on cerebral blood flow after the use of HBOT is mainly attributed to a decrease in the concentration of nitric oxide in the brain, as well as to an inclination in the production of reactive oxygen species [20]. Following this treatment, dependent improvements in general motor function, cognitive and behavioral tests, neurological function and locomotor coordination have been observed [8].

Proteomic studies, have observed that in acute TBI there is a decrease in the levels of pAkt/Akt, pGSK3β/GSK3β, and β-catenin, which facilitates neuronal apoptosis. He et al [13]. demonstrated increase in these proteins after instituting HBOT [13].

Table 1. Neuroprotective effects of hyperbaric oxygen therapy

Reduces inflammation	Induces Bcl-2 and Bcl-xl, reduces Cas-3
Inhibits neutrophil adhesion to endothelial cells	Inhibits permeability of mPTP
Decreases IL-8, TNF-α and MMP-9; increases IL-10	Decreases endothelin levels and regulates blood flow
Inhibits TLR4 and NF-κB expression	Reduces intracranial pressure
Inhibits apoptosis	Promotes neurogenesis and angiogenesis.
Increases PaO2 of brain tissue.	Enhances Nrf2 and HO-1
Preserves tissue metabolism	

Importance

Neuroinflammation is well established as a key secondary injury mechanism after TBI, and has long been considered to contribute to sustained damage after brain injury [5,21]. With HBOT, the effect of high pressure, increased solubility and O2 diffusion characters are expected to improve oxygenation, modulation of inflammation and immune function, as well as promote angiogenesis [1].

Comprehensive management of traumatic brain injury generally aims at maintaining oxygenation and perfusion, so hyperbaric oxygen has been proposed as a complementary therapy for TBI, both for the preservation of the functional capacity of the affected person, as well as for the increase in survival rate [2,6,9].

Efficacy

The prognosis of traumatic brain injury clearly depends on the cell death and survival processes occurring within the injured tissues, so neuroprotective therapies aim to improve function within the remaining viable perilesional brain tissue [16].

Increased oxygen supply under hyperbaric conditions facilitates oxygen diffusion into the injured tissue, improving cellular energy metabolism, which attenuates cell signaling and cytosolic ischemic cascades, thereby reducing programmed cell death and subsequent necrosis [22]. Many studies have consistently corroborated that HBOT compared with standard care significantly improves markers of oxidative metabolism in the relatively uninjured brain [22].

HBOT may also counteract vasodilation of capillaries within hypoxic tissues, thus minimizing extravascular fluid accumulation, reducing cerebral vasogenic edema and intracranial pressure [16]. This is why it has been postulated that HBOT stimulates the restoration of antioxidant, angiogenic, neurogenic and anti-inflammatory gene expression. This translates into greater neurological recovery, as evidenced by the improvement of the Glasgow score [5,13,23]. To obtain the benefits described above, this therapy should be started within the first hours, and several sessions should be established [5].

Generalities

HBOT is a therapeutic option that consists in the inhalation of 100% oxygen, in a sealed hermetic chamber that increases the pressure to more than one absolute atmosphere (ATA); (ATA=101.3kPa) [1,3,4,5,16,24]. Generally, a pressurization of 1.5-3.0 ATA is used for one or more times a day, for one or two hours [25]. This ensures the administration of a higher partial pressure of oxygen in the blood, improving mitochondrial metabolism and tissue oxygenation [5,6,16]. The benefits found in this therapy have allowed recommending its use in a large number of pathological conditions (Table 2), which is increasing over the years.

HBOT allows hemoglobin to be saturated to 100% and the volume of oxygen fraction bound to plasma to be elevated [4,16]. The latter can be used more easily than that bound to hemoglobin, so that oxygen is supplied even in conditions with erythrocyte deficit; therefore, HBOT causes an increase in oxygen transport in the blood, increasing the force of oxygen diffusion in the tissues [16].

Table 2. Indications for hyperbaric oxygen therapy

Stroke [6]	Decompression sickness [6,16]
Anoxic brain injury [6]	Carbon monoxide poisoning
Cerebral edema*[7]	Minimization of tissue damage induced by radiotherapy [4,16]
Ictus [7]	Enhancing skin grafts [4,16]
Spinal cord injury*[7]	Autism* [16]
Acute central retinal artery insufficiency*[7]	Multiple sclerosis* [16]
Traumatic ischemia [7]	Air or gas embolism [4]
Gas gangrene [4]	Compartment syndrome [4]
Intracranial abscess [4]	Osteomyelitis [4]
Burns [4]	Wounds [4]

Non-approved use

HBOT has been in use for more than 50 years, but its application in the treatment of traumatic brain injury has been performed since the early 1960s [7]. In 1966, the first study reporting the neuroprotective effect of this therapy in rats was published by Coe & Hayes [26]. Almost immediately, Dunn & Lawson [27]. demonstrated reduced mortality in a canine model with cerebral contusion, and since then, studies on the effect of HBOT on blood flow, cerebral edema and intracranial pressure have been carried out.

Conclusion

Traumatic brain injury is a common health problem that causes permanent sequelae and considerably decreases the functional capacity of the sufferer. Unfortunately, to date there is no treatment or intervention that fully ensures neurological functionality. Hyperbaric oxygen therapy is a therapeutic option with the potential to decrease neuronal death by improving oxygen supply to the injured brain, thus controlling inflammation and apoptotic processes. The effectiveness of the intervention, however, depends on prompt medical attention and constant monitoring of hemodynamic and neurological variables.

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