

# HYPERBARIC OXYGEN THERAPY IN TRAUMATIC BRAIN INJURY

Daniel KRAUS<sup>1\*</sup> – Juraj ČELKO<sup>2</sup>

<sup>1</sup> Faculty Hospital Trenčín, Legionárska 28, 91171 Trenčín, Slovak Republic

<sup>2</sup> Faculty of Healthcare, Alexander Dubček University of Trenčín, Študentská 2, 911 50 Trenčín, Slovak Republic

\*Corresponding author E-mail address: daniel.kraus@fntn.sk

## Abstract

**Background:** Traumatic brain injury (TBI) is the leading cause for mortality and morbidity for millions of young people around the world every year. A decrease of oxygen supply in TBI has devastating effects on the injured brain tissue.

**Objectives:** This study is aimed to determine whether the hyperbaric oxygen therapy (HBOT) can be suggested as a scientific and effective treatment for TBI.

**Methods:** In the review article, we present findings from studies published in electronic databases and journals until the end of 2016 aimed at the effect of HBOT in TBI and we demonstrate two patients with TBI that were treated with HBOT in the hospital of Trenčín.

**Results:** Many articles have been published that demonstrate HBOT could affect brain tissue hypoxia thereby avoiding neuronal cell death through increased cerebral oxygen metabolism. Early and timely HBOT intervention can have a more robust effect than delayed intervention, but HBOT is also effective in repairing an injured brain even long after that injury took place. In two patients that we demonstrate in this article, daily application of HBOT was prescribed not only while in hospital but at certain intervals also later and it contributed significantly to restoration of neurological and cognitive functions.

**Keywords:** Hyperbaric oxygen therapy. Traumatic brain injury. Concussion. Clinical trials.

## 1 Introduction

Traumatic brain injury (TBI) is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile. Consequently to the injury, brain function is temporarily or permanently impaired and structural damage may or may not be detectable with current imaging technology. TBI is usually classified based on severity, anatomical features of the injury, and the cause of the injury. The severity is assessed according to the loss of consciousness duration, the post-traumatic amnesia, and the Glasgow coma scale (GCS) grading of the level of consciousness [1].

The GCS is used to grade TBI as mild, moderate, or severe. Of all severities of TBI, an estimated 75-85% are categorized as mild TBI (mTBI) with GCS score of 13 to 15. Mild TBI occurs in a wide variety of activities including sports, such as boxing, American football, rugby, soccer, cheerleading, ice hockey, and wrestling; military service; and in association with other exposures such as poorly controlled epilepsy, head banging, and physical abuse. There is often full neurologic recovery after mTBI; however, 15-30% of subjects develop prolonged neurocognitive and behavioral changes. In the US, it is estimated that 1,6-3,8 million concussions occur annually. Concussion is especially frequent in American football, where 4,5% of high school, 6,3% of collegiate, and 6,6% of professional football players are diagnosed with at least one concussion per season. The true frequency of concussion is likely far greater because concussions are routinely under-recognized, under-reported and typically resolve spontaneously without medical care [2].

In moderate traumatic brain injury (GCS 3-13), the patient is initially lethargic or stuporous, and in severe TBI (GCS 3-8), the patient is comatose, unable to open the eyes or follow commands. Patients with severe TBI are at high risk for secondary brain injury including hypotension, hypoxemia, and brain swelling. In the lower ranges of GCS score (3-9), primarily associated with severe TBI, there is a direct linear relation to a poor outcome, including severe neurologic disability, vegetative state, and death. Advancing age, particularly over the age of 60 years, is also associated with an increased risk of a poor outcome.

The severity of TBI can also be categorized by the duration of level of consciousness (LOC) and post-traumatic amnesia (PTA), measures that are reported to have better correlation with patient outcome than GCS. Mild TBI is defined as LOC of less than 1 hour and PTA for less than 24 hours, moderate TBI is defined by LOC between 1 and 24 hours or PTA for 1-7 days, and severe TBI by LOC for more than 24 hours or PTA for more than 1 week [3].

TBI, particularly mTBI, has been largely overlooked as a major health concern until very recently. It is increasingly clear that TBI is a process and not a static injury, and that prolonged symptoms in TBI survivors represent functional and structural damage [4]. Retired professional football players who sustained three or more concussions were found to report more cognitive symptoms including a threefold increase in significant memory impairment, and a fivefold increase in diagnosed mild cognitive impairment compared to retired players without a history of concussion. Brain trauma experiences in sport has also been linked to disturbances in mood. Retired professional football players who experience three or more concussions reported a threefold increase in diagnosed depression [5]. Head injury increased the risk of Alzheimer's disease and the risk increased with increasing severity

of the head injury, no increased risk was found for veterans who had a mild TBI [6]. The frequency of head trauma was significantly higher in Parkinson's disease cases.

Although many preclinical and clinical trials have been carried out to explore underlying pathophysiology of TBI, few effective treatment options have been used to ameliorate the prognosis of TBI, particularly with regard to the recovery of neurological deficits. Surgical treatment, such as hematoma or contusion focus removal, is used for saving lives, but cannot improve the prognosis [7]. The general consensus is that efficient treatment should focus on secondary brain injury. Previously, therapies concentrated on the stabilization of blood and intracranial pressure. They generally involved the administration of neuroprotective drugs as well as rehabilitation training, though they neglected the hypoxic state of brain tissue after TBI. Several studies have shown that secondary ischemic injury exists in brain tissue in the early stages of TBI and that is an important contributor to morbidity and mortality. Therefore, an oxygen-directed therapy may contribute to reducing mortality and thus improve the outcome for TBI patients [8].

## 2 Normobaric oxygen therapy and TBI

There are numerous studies that demonstrate enhanced clinical outcomes by treatment with normobaric oxygen (NBOT) [9]. Much of the enthusiasm for use of NBOT is based on a prospective study of severe TBI patients. Narotam and colleagues [10] evaluated brain tissue oxygen concentrations in patients with severe TBI. Using Licox oxygen probes, 139 patients were studied using a pO<sub>2</sub> protocol that maintained brain oxygen levels to > 20 mm Hg. They elegantly demonstrated that normobaric oxygen therapy significantly reduced mortality, but moreover, they showed improved clinical outcomes at 6 months post-severe TBI. A similar study found that hyperoxia improved the cerebral metabolic rate of oxygen in severe TBI patients using O<sub>15</sub>-positron emission tomography, but they did not compare to HBOT treated patients [11].

## 3 Hyperbaric oxygen therapy and TBI

Hyperbaric oxygen therapy (HBOT) is a modern therapeutic method in which the patient is exposed to 100% oxygen at a pressure of above 1 atmosphere (ATA). This results in an increase of blood oxygen level which can reach into ischemic areas deeper than at a pressure of 1 ATA. The treatment aims to support healing and regeneration processes of individual cells and tissues in the body [12, 13].

Based on evidence that NBOT of human TBI patients appeared to have similar outcomes as patients who underwent HBOT, a follow-up study was conducted to compare two groups after severe TBI to assess the efficacy of therapy [14]. The study design included controls (standard of care), normobaric (3 hrs 100% O<sub>2</sub>) and HBOT (1,5 ATA for 60 min) that received their initial treatment within 24 hrs of a severe TBI. Treatments were conducted daily for 3 consecutive days. The pO<sub>2</sub> levels within the brain were nearly 3 fold higher in the HBOT compared to the NBOT groups and significantly different from controls. In the HBOT group they found increased cerebral metabolic rate of oxygen, decreased lactate and decreased intracranial pressure. They also reported that HBOT increased cerebral blood flow. Perhaps the most important finding was that an indicator of mitochondrial dysfunction, lactate/pyruvate ratios were significantly decreased only in the HBOT group. Thus, HBOT for severe TBI, appears to improve cellular survival which was not observed in NBOT group.

The role of the transport system is to ensure a sufficient partial pressure of oxygen at capillaries ends in order to affect a passive diffusion of oxygen into the mitochondria. A natural regional flow through the body is variable, organs such as heart and brain take more oxygen from blood compared to other organs. Brain's oxygen consumption may be up to 20% of the total body consumption [15]. Cells in the central nervous system rely exclusively on aerobic metabolism and need a high supply of oxygen. In the absence of oxygen neuronal cells inevitably die. HBOT reduces the ischemic loss of neurons in the hippocampus and improves the neurobehavioral outcome [16, 14].

Under normal healthy conditions, brain metabolism reaches the upper limit of oxygen consumption, which makes it dependent on cerebral blood flow. At each time point, the cerebral blood flow shifts to more active regions (task-dependent) at the expense of other, less active regions. These physiological changes in cerebral blood flow can be easily seen in functional magnetic resonance imaging. Major insults to the brain, such as intracerebral hemorrhage, ischemic stroke, or traumatic brain injury, compromise cerebral blood flow and further decrease the oxygen delivery to the „non-active“, injured brain tissue. In a hypobaric environment, oxygen delivery decreases below the minimal metabolic needs [17].

HBOT likely treats TBI via several different pathophysiological mechanisms [18]: HBOT increases arterial oxygen pressure and brain tissue oxygen levels; vasoconstriction capacity leads to low cerebral blood flow, which is accompanied by improving consciousness as the result of edema and intracranial pressure reduction; HBOT accelerates collateral circulation to protect neurons from ischemic death and also repairs the damaged microvessels, thereby simultaneously stimulating angiogenesis and neurogenesis; HBOT can prevent a large microthrombus from forming, while also simultaneously promoting their absorption. The underlying potential of neurological function recovery in TBI patients decreases if the intervention with HBOT is delayed. Therefore, it is essential that HBOT is used in patients as soon as possible.

On the other hand, many articles have been published in the last decade that demonstrate hyperbaric oxygen is effective in repairing an injured brain even long after that injury took place. One of the most notable was the article published by Harch [19] et al using the protocol forty 60 min treatments at 1,5 atmospheres. The blast-induced war veterans experienced a 15 point IQ increase ( $p < 0,001$ ), 39% reduction in post-traumatic stress disorder symptoms and 51% decrease in depression. There are now 20 US military veterans committing suicide every day directly related to TBI/PTSD. Even National Football League veterans are starting to commit suicide. The clinical trial called National Brain Injury Rescue and Rehabilitation project showed HBOT can virtually eliminate suicidality in this population once they are treated with HBOT, while reducing depression by 51%. Several authors believe that the number of suicides could be significantly reduced by greater use of HBOT in these conditions since antidepressants are modestly effective in reducing the symptoms of severe depression [20].

In animal studies, it was found that HBOT exerts a neuroprotective effect and improves prognosis following blast-induced TBI by promoting the metabolism of local neurons, inhibiting the accumulation of inflammatory cells. Furthermore, timely intervention, i.e. within 1 week of injury, may be more conducive to improving the prognosis of patients with blast-induced TBI [21]. The aim of the study was to investigate the efficacy of hyperbaric oxygen in secondary brain injury after trauma and its mechanism in a rat model. 60 rats were randomly divided into three groups – the sham group, the untreated traumatic brain injury group and the hyperbaric oxygen-treated TBI group. The neurological function of the rats was evaluated 12 and 24 hours after TBI modeling. HBOT reduced apoptosis of the neurons and improved the neurological function of the rats ( $p < 0,05$ ) [22]. Early and timely HBOT intervention can have a more robust effect than delayed intervention, as hypoxia-inducible factor 1- $\alpha$  is inhibited and the percentage of apoptotic cells in brain tissue declines dramatically [23]. Trauma-associated neurological impairment regressed significantly following 3 weeks of repeated HBOT, a process that is mediated by pronounced remyelination in the ipsilateral injured cortex, as substantiated by the associated recovery of sensorimotor function [24]. In the acute stage, HBOT may improve the outcome of TBI in rats by inhibiting activated inflammation and gliosis, while both angiogenesis and neurogenesis are stimulated [25]. A systematic search of literature published prior to September 2015 was performed to evaluate the benefit of HBOT in animal studies of middle cerebral artery occlusion. HBOT had a neuro-protective effect and improved survival in animal models especially in animals given more than 6 hours of HBOT and when given immediately after middle cerebral artery occlusion with 2,0 ATA [26].

Clinical trials have shown that hypoxic episodes are common events after severe TBI, and most are independent of intracranial pressure alterations. In addition, most hypoxic episodes occur while cerebral perfusion and mean arterial pressure are within the accepted range. When cerebral perfusion pressure is  $< 60$  mm Hg, the frequency of hypoxic episodes increases significantly. Furthermore, an increased frequency of hypoxic episodes is associated with a poor functional outcome [27].

#### 4 Objective

To establish the effect of HBOT on TBI inpatients at the Department of Anesthesiology and Intensive Care /DAIC/, Teaching Hospital in Trenčín.

#### 5 Methods

The effect of repeated series of regular HBOT application has been observed in two TBI patients during their hospitalization at DAIC and when transferred to the neurological department, after rehabilitation treatment at the National Rehabilitation Centre Kováčová and in home care. The development of clinical symptoms was evaluated, especially in the area of intensive care medicine, neurology and psychology.

#### 6 Case report 1

Patient M.Ď., born in 1990, was on 26.05.2014 admitted to DAIC Nové Zámky with chest trauma and severe cranial trauma after hitting the post with motorcycle (without helmet). Following consultation with the neurosurgeon, conservative approach has been chosen, therefore he was transferred to DAIC Trenčín on 09.06.2014. Comatose patient was on mechanical ventilation, tracheostomy applied. CT finding showed basilar skull fracture. dx., frontal contusion foci bilaterally, calvarial fracture, hemothorax l.dx., pneumothorax bilaterally. During treatment, the patient is gradually coming to vigil coma and later severe qualitative consciousness disturbance remains with perceptual expressive aphasia. Intracranial pressure sensor introduced in the patient showed values lower than 20 Torr. On 19.06.2014 MRI brain findings showed frontal contusion foci bilaterally at the stage of organization, small hemorrhages F-P-T bilaterally, numerous contusion changes T-P l.sin. and in corpus callosum.

On the 20<sup>th</sup> day of hospitalization, daily treatment in hyperbaric chamber initiated at a pressure of 2 ATA for one hour. The patient improved slightly, began to react adequately, but remained severe spastic hemiparesis with behavioral disorder and restlessness. On 09.07. he was transferred to the neurological department where he continued with HBOT up to a total dose of 20 applications. On 22.07. discharged from the neurological department to home care; treatment in National Rehabilitation Centre Kováčová scheduled. General condition improved, right

upper limb spasticity subsided, improved motivity and strength in the right upper and lower limbs. With the support of two people he is able to walk about 3 to 5 meters. Total expressive aphasia continues, organic psychosyndrome manifestations are present, prefrontal symptomatology with motoric restlessness. Sphincters are not under control. Afebrile, pressure stabilized.

Within out-patient care the patient took HBOT in March 2015 (16x), in September 2015 (16x) and in April 2016 (19x). His cognitive and neurological functions improved gradually and in July 2016 he is fully oriented, with minimal neurologic deficit. He has a good memory and according to a psychologist, his intelligence is slightly above average. The patient has an adequate gait perimeter and is ready to start work.

## 7 Case report 2

Patient Z.O., born in 1993, had an accident as motorcyclist on 01.10.2015. He was found lying in a ditch, wheezing, no precise indication as to how long he was there without help. He was intubated by an emergency surgeon, connected to controlled ventilation and brought to DAIC Trenčín. CT shows a small subdural hematoma frontal l.sin., bilateral convexal subarachnoid hemorrhage, bilateral brain edema and bilateral pulmonary contusion. The patient's condition consulted with neurosurgeon who suggests conservative approach. Neuroprotective therapy initiated, controlled ventilation, tracheostomy, for digestion disorder parenteral nutrition administered and later percutaneous gastrostomy. Since the patient had swallowing disorder, he was fed by gavage. Patient's condition is gradually improving, he does not need ventilation, regained cough reflex, therefore tracheostomy was removed. On 19.10. HBOT commenced, pressure of 2 ATA, duration of one hour, a total of 8 times. Condition improved significantly, percutaneous gastrostomy could be removed in stages. On 21. 10. he was transferred to the traumatic department. On 3.12. he was discharged to home care; treatment in National Rehabilitation Centre Kováčová scheduled. After a four week rehabilitation in Kováčová neurological finding improved significantly, prescribed 16x HBOT, condition gradually improved almost ad integrum. Psychologist assessed his condition as behavior modification, he made significant progress in intelligence tests, calmed down, can take care of himself, able to clean up, no neurological deficit.

## 8 Discussion and conclusion

The modern age of hyperbaric medicine began in 1973 using HBOT in the treatment of decompression sickness. However, today few know about hyperbaric oxygen's effect on the body and medical conditions outside of diving medicine and wound care centers. Because no patent is possible on oxygen (or any other element), there is no profit to spark a large pharmaceutical interest to prove or promote it [20]. Research of HBOT in a variety of TBI models has shown neuroprotective effects in the absence of increased oxygen toxicity when administered at pressures less than 3 ATA. Although both NBOT and HBOT can be neuroprotective, HBOT exerts more robust and long-lasting effects in the absence of pulmonary or cerebral oxygen toxicity. The improved tissue oxygenation and cellular metabolism, anti-apoptotic as well as anti-inflammatory effects may constitute the multiple and complementary mechanisms underlying HBOT-induced neuroprotection [28]. HBOT might initiate a cellular and vascular repair mechanism and improve cerebral vascular flow [29, 30].

In patients included in case reports, HBOT contributed significantly to restoration of neurological and cognitive functions. Following the results of numerous studies demonstrating that HBOT is effective in repairing an injured brain even long after the injury took place, daily administration of HBOT in our patients was prescribed not only while in hospital but also later at certain intervals within out-patient care, and their health was objectively improving. For optimal recovery of neurological functions in TBI HBOT should be applied as soon as possible, which will require some organizational arrangements at our workplace.

Increasing evidence has shown that HBOT is a key contributor in the treatment of TBI and occupies an important place in modern neurosurgery. Apart from TBI, other cerebrovascular diseases, such as intracerebral hemorrhage and high-grade subarachnoid hemorrhage, also have significant therapeutical indications to improve the prognosis. Zhu et al [31] have shown in their study that the therapeutic window is very narrow and any slight decrease in oxygen delivery has devastating effects on the injured brain tissue. HBOT may well be the sought-after tool, both effective and simple, for improving brain tissue oxygenation and brain metabolism needed for the regenerative processes.

Despite the favorable outcome of many trials assessing the effect of HBOT in TBI patients it is difficult to achieve a clear agreement due to difference in external conditions [32]: the lack of conformity of patient's clinical data in the literature may affect our judgment of the therapeutical value of HBOT; the nonstandard intervention methods used in primary health care increase the risk of complications; obtaining a large sample is extremely costly, especially for smaller research centers. The fewer the cases included in a trial, the lower the credibility of the conclusions drawn from it. Although clinical trials face many ethical and funding challenges, what is to be gained from them justifies their continued use. In order to provide clinically beneficial therapies, further research should be undertaken into the mechanisms and efficacy of HBOT. It is also necessary to objectify long-term effects of HBOT both in severe as well as mild TBI.

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