THE USE OF HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF PATIENTS AFTER TRAUMATIC BRAIN INJURY. REVIEW OF RESEARCH

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ABSTRACT

Introduction A traumatic brain injury (TBI) may lead to permanent or temporary impairment of cognitive, sensorimotor and psychosocial functions with accompanying consciousness disorders. The most common primary pathology is the diffused axonal injury. In an early phase, despite an elevated demand of energy of cerebral tissues, the oxygen supply and its diffusion to tissues become reduced. Hyperbaric oxygen therapy (HBOT) is a supplementary treatment based on inhaling 100% oxygen at an increased pressure. HBOT contributes to a significant increase in oxygen pressure in the blood. This process may considerably increase the extent of oxygen diffusion from capillary vessels into the neighbouring hypoxic cells, thus facilitating their metabolism.
Objective. The objective of the study was to conduct a review of available literature aimed at finding preclinical and clinical research assessing the efficacy of HBOT in the therapeutic process related to TBI.
Material and methods. The following electronic full-text bibliographic databases were searched by entering the following key words: *hyperbaric oxygen therapy and traumatic brain injury: EBSCO host Web, Wiley Online Library, Springer Link, Science Direct* and *Medline.* The inclusion criteria encompassed preclinical and clinical examinations verifying the therapeutic efficacy of HBOT at various TBI stages and intensification levels in adults. The evaluated papers were articles published in Polish and English. The exclusion criteria concerned research conducted in the form of case studies and reports.
Results. The final review involved ten preclinical studies published in the years 2006-2014 and seven clinical studies from 2008-2013.
Conclusions. The results of preclinical studies indicated a considerable medical potential of HBOT. An analysis of clinical studies, on the other hand, revealed equivocal and somewhat contradictory final results. It is necessary to conduct further prospective randomised research that could help to evaluate the real therapeutic effect of HBOT in patients after TBI.
Key words: traumatic brain injury, hyperbaric oxygen therapy, research review.

ARTICLE INFO

PolHypRes 2014 Vol. 46 Issue 1 pp. 7 – 26

ISSN: 1734-7009 **eISSN:** 2084-0535

DOI: HTTP://DX.DOI.ORG/10.13006/PHR.46.1
Pages: 21, figures: 0, tables: 2.

page www of the periodical: www.phr.net.pl

Publisher
Polish Hyperbaric Medicine and Technology Society

INTRODUCTION

Traumatic brain injury (TBI) is defined as non-degenerative acquired brain damage due to external mechanical forces, which may lead to permanent or momentary impairment of cognitive, sensorimotor and psychosocial functions with accompanying consciousness disorders [1]. TBI is a common health care issue. A review of epidemiological studies carried out in Europe indicates that the hospitalisation rate in relation to TBI amounts to 235 out of 100 thousand cases. [2] Moreover, according to a meta-analysis by Frost et al. [3], 2600 out of 25 thousand examined adults had suffered from a brain injury in the past. It should be noted that the incidence of the discussed disorder is estimated only on the basis of hospitalised cases, without considering the injured that failed to report to the health services. Thus, it may suggest that the actual incidence may in fact be several times higher.

Diffuse axonal injury (DAI) is one of the most frequent primary pathologies connected with TBI. The dominant symptoms comprise cognitive disorders, mainly involving the functions of memory, focus, information processing rate and executive functions. All of them are localised in various brain areas. The dispersed nature of injuries in TBI is difficult to detect with the common neuroimaging methods, i.e. Computer Tomography (CT) and Magnetic Resonance Imaging (MRI), that is why such disorders are commonly detected with cognitive impairment and quality of life tests [4,5]. Secondary pathologies of TBI include ischaemia, mild oedema and other inflammatory processes resulting in an impairment of regenerative processes caused by growing tissue hypoxia [5].

Ischaemia is the main reason for secondary brain damage in TBI with death being a potential consequence of severe damage [6]. Disturbances in O_2 distribution to cerebral tissues cause a conversion from oxygen metabolism to anaerobic metabolism [7]. Anaerobic metabolism results in acidosis and exhaustion of cellular energy reserves. The demand of energy production is no longer satisfied, cerebral cells lose their ability to maintain ion homeostasis, which leads to an increased intracellular concentration of calcium [8]. The combination of cellular acidosis and an excess concentration of calcium activate intracellular processes, causing the occurrence
of oxygen free radicals which go on to damage, among other things, the cellular membranes [9]. High calcium levels also leads to its absorption into mitochondria causing an impairment in ATP phosphorylation and further decrease in oxygen metabolism [10]. In the early phase, despite an elevated energy demand of cerebral tissues, the oxygen supply and its diffusion to tissues become reduced [11,12].

Hyperbaric oxygen therapy (HBOT) consists of a patient's inhalation of 100% oxygen whilst inside a specially constructed pressure treatment chamber. The pressure exerted during an exposure is expressed with the sum of atmospheric pressure and the pressure within the chamber (ATA - atmosphere absolute) [13]. It has been established that it should reach at least 1.4 ATA. However, the dose believed to be more therapeutically effective ranges from 2.4 to 3.0 ATA [14,15]. An HBOT intervention contributes to a significant increase in oxygen pressure in the blood. Its physical solubility is then 20 times higher as compared with normal pressure conditions. Oxygen that is dissolved in the blood plasma may be used by tissues in a more efficient manner than the oxygen bonded with haemoglobin despite the absence of erythrocites [16]. Such processes may considerably increase the extent of oxygen diffusion from capillary vessels into the neighbouring hypoxic cells, thus facilitating their metabolism [17-19].

The guidelines, regarding patient qualification for treatment in a hyperbaric chamber, are defined by the National Health Fund based on a list of recommendations of the European Society of Hyperbaric Medicine and the Society of Underwater and Hyperbaric Medicine. The list of officially treated medical conditions does not encompass

neurological and psychiatric ailments due to a lack of a sufficient number of reliable randomised prospective researches confirming efficacy of the method [20]. Currently, intense clinical studies are conducted with the aim of evaluating the safety and efficacy of HBOT in relation to brain injuries and psychological disorders.

The first clinical observation that presented a therapeutic result in patients with TBI after HBOT was carried out by Fasano et al. 50 years ago [21]. At present, HBOT is believed to have a neuroprotective function through: the facilitation of metabolic processes in the brain [22,23], an increase in the permeability of the blood-brain barrier, reduction of the oedema [24], decrease in intracranial pressure [25], suppression of proinflammatory reactions [26] and prevention of cell apoptosis [27,28]. The safety of HBOT has been tested with regard to all age groups and both sexes, including pregnant women [29] and neonates [30]. The method is perceived as relatively safe. The most common HBOT-related complication is an earache or a discomfort induced by pressure compensation in the middle ear, and concerns approximately 17% of cases. Statistically less frequent complications, 3.8%, include barotraumatic injuries of the middle ear, nasal sinuses, internal ear, lungs or teeth [31]. Another issue is claustrophobia, occurring in one out of 50 patients subjected to HBOT [32]. In a repeatable treatment of over 20 exposures it is possible to observe temporary impairment of distance vision, which yields after 6-8 weeks from treatment completion. This mainly concerns patients with myopia. During the research it was observed that the impairment was intensified when applying pressure above 2 ATA [33,34]. The temporary, non-specific symptoms, which diminished naturally after 4-6 weeks from HBOT completion also included abdominal pain, nausea, vomiting, diarrhoea, tingling and stiffening sensations [32,35].

OBJECTIVE

The objective of the study was to conduct a review of available literature aimed at finding preclinical and clinical research assessing the efficacy of HBOT in the therapeutic process related to TBI.

MATERIAL AND METHODS

The following electronic full-text bibliographic databases were searched by entering the following key words hyperbaric oxygen therapy and traumatic brain injury: EBSCO host Web, Wiley Online Library, Springer Link, Science Direct and Medline. The inclusion criteria encompassed preclinical and clinical control and observatory examinations verifying the therapeutic efficacy of HBOT at various TBI stages and intensification levels in adults. The selected studies used various HBOT protocols and methods to evaluate its health effects. The evaluation was concerned only with articles published in Polish and English in full- text versions in reviewed magazines with international coverage from the years 2006-2014. The applied exclusion criteria, on the other, concerned researches conducted in the form of case studies and reports. An analysis of clinical effectiveness of HBOT in the selected studies was conducted in accordance with the PICO principle which refers to four elements, i.e. population, intervention, comparator and outcome.

RESULTS

The final review involved ten preclinical studies published in the years 2006-2014 and seven clinical studies from 2008-2013.

HBOT IN ANIMALS AFTER TBI

Based on the most recent experimental research we see the significance of the effect of an inflammatory process on secondary brain damage resulting from TBI. The functioning of HBOT has not been completely recognised; the process still raises some controversies in scientific circles. We distinguish several factors which play a crucial role in HBOT, i.e.: neutrophils, metalloproteinases (MMPs), caspases and hypoxia-inducible factor 1-α (HIF-1 α). Based on the work by Vlodavsky et al. we may note the important role of MMPs. MMPs take part in pathological and physiological remodelling of tissues. Additionally, MMPs-2 and -9 are involved in degenerative and repair processes in tissues, signal transduction, reconstruction of areas affected by an inflammatory process. MMP activity is regulated with tissue inhibitors of metalloproteinases (TIMPs).

After an injury Neutrophils lead to an occlusion of microcirculation, releasing oxygen free radicals, cytolitic proteases and proinflammatory cytokines. An inflammatory infiltration composed of myeloperoxidases-neutrophils was larger in animals treated with HBOT as compared with those that did not receive treatment. Statistical significance was visible in the quantitative reduction of MMPs-9 [37]. Some of the experimental data indicated HBOT's role in the reduction in the level of caspases 9 and 3 due to mitochondrial protective mechanisms. Caspases initiate and manage the process of apoptosis, which is significant with regard to neuroprotection in the penumbra. On the one an increase in inflammatory cells enhances MMP activity [36,37]. Neutrophils lead to an occlusion of microcirculation, releasing oxygen free radicals, cytolitic proteases and proinflammatory cytokines. An inflammatory infiltration composed of myeloperoxidases-neutrophils was larger in animals treated with HBOT as compared with those that did not receive treatment. Statistical significance was visible in the quantitative reduction of MMPs-9 [37].

Some of the experimental data indicated HBOT's role in the reduction in the level of caspases 9 and 3 due to mitochondrial protective mechanisms. Caspases initiate and manage the process of apoptosis, which is significant with regard to neuroprotection in the penumbra. On the one hand, brain damage leads to an activation of microglia, which intensifies the proinflammatory response. The modulation of reactive microglia may be applied in treating neurological conditions. Research on rats indicated that HBOT contained the expression of TNF-α, neuron apoptosis and microglia activation. Even 8h after a brain injury HBOT maintains its therapeutic effect. [19]

The research on 500 rats showed that HBOT reduced apoptosis and HIF 1 α expression. A decreased level of apoptosis may be connected with a reduction in intracellular calcium, an improvement in energy balance and an elevated production of antioxidants [39]. Furthermore, the research proves a positive effect on memory loss induced by TBI. HBOT causes stenosis of blood vessels and a decrease in cerebral blood flow (CBF), which results in a reduced oedema. Yang et al. expressed this by introducing the Evans Blue index (EB) and measuring water content in the brain [40]. The authors used MR with contrast (MRI-DCM) combined with diffusion weighted imaging (DWI) in research on rabbits after TBI to depict changes occurring in a damaged tissue, which provided valuable information on clinical application of HBOT.

The number of points in the veterinary coma scale (VCS) was higher in the group HBOT + TBI than with TBI determined within 30 days, which suggests a positive effect of HBOT. The VCS evaluates the motor activity of the body, eyes and respiratory activity, thus indicating a certain similarity to the Glasgow scale [41]. On the other hand, the researchers studied the medicinal effect of HBOT in rats following unilateral ablation through an increase in the neuroplasticity that indicated statistical significance. This increase may be

translated into an improvement in motor functions (muscle tone and coordination) in the animals, as examined with the Beam walking test and the Grip strength test [42].

Tab. 1.

Summarised results of preclinical research with the use of HBOT after TBI.

Research	Species	Method	Dosage	Time	End point
Yang et al. (2014)	Rats	After treatment	1.5 ATA for 90 min.	1 once a day, 15 sessions	↑ neurobehavioral functions ↓ neuron apoptosis ↓ *Assay TUNEL*
Wei et al. (2014)	Rabbits	After treatment	2.5 ATA for 60 min.	10 per day, 7 sessions	↑ neurobehavioral functions
Lim et al. (2013)	Rats	After treatment	2.0 ATA for 60 min.	once	↑ neurobehavioral functions ↓ neuron apoptosis ↓ ischemic area
Lin et al. (2012)	Rats	After treatment	2.0 ATA for 60 min.	1 per day, 3 sessions	↑ neurobehavioral functions ↓ ischemic area ↓ *Assay TUNEL*
Brkic et al. (2012)	Rats	After treatment	2.5 ATA for 60 min.	1 per day, 10 sessions	↑ GAP43 and SYP expression ↑ motor functions
Wang et al. (2010)	Rats	After treatment	3.0 ATA for 60 min.	3 or 5 per day, 5 sessions	↑ neurobehavioral functions ↓ *assay TUNEL*
Hu et al. (2010)	Rats	Before treatment	2.5 ATA for 60 min.	1 per day, 8 sessions	↑ neurobehavioral functions ↑ rCBR
Harch et al. (2007)	Rats	After treatment	1.5 ATA for 90 min.	1 per day, 7 sessions	↑ vascular density in hippocampus ↑ cognitive functions
Vlodavsky et al. (2006)	Rats	After treatment	2.8 ATA for 45 min.	2 per day, 3 sessions	↓ *Assay TUNEL*

HBOT IN ANIMALS AFTER TBI

The qualified studies encompassed patients with various forms of TBI, with three of them being concerned with moderate TBI, another three with severe TBI, and 1 with patients without TBI diversification. The number of patients in each trial ranged from 20 to 90. The interventions were applied after different periods from a TBI incident. Two of the studies evaluated patients in an acute condition 24-48 h from TBI occurrence, another 3 examinations involved patients in a chronic condition maintained from 1 month to 5 years, whereas the rest lacked information regarding the patients' condition. Oxygen dosage was largely diversified in particular examinations and reached from 1.5 to 2.4 ATA, with an intervention time ranging between 60 to 90 min. In one instance only one compression was carried out, whereas in the remaining cases the number of compressions oscillated around 20 to 40 procedures. The control group received standard treatment during five procedures, whereas the remaining two procedures involved the use of air

breathed at a pressure of 1.3 ATA. The analysis of the conducted studies revealed that the interest in the application of HBOT in treating TBI was based on an assumption that cellular hypoxia, oedema and apoptosis played a significant role in its pathogenesis.

Lin et al. [43] evaluated in a prospective study the efficiency of the HBOT method among patients with severe TBI, on average 27.5 +/- 5.8 days from the injury. The research comprised 44 patients, with 22 of them subjected to HBOT intervention of 2.0 ATA for the period of 90 min, once a day, for 20 days, whereas the remaining 22 patients were treated with the use of standard procedures. The end result was measured with the Glasgow Coma Scale (GCS) and the Glasgow Outcome Scale (GOS). The initial means according to the GCS for both groups on the day of the patients' admittance to hospital reached 8.0 for the researched group and 7.9 for the control group. After carrying out standard life-saving procedures, the GCS index revealed an increase in both groups.

The result for the researched group was 11.1, whereas the same index for the control group amounted to 10.4 points. The research procedure was initiated after the stabilisation of post-injury condition in patients. Final results indicated an improvement in the HBOT group to 13.5 points, whereas the index value of the control group was equal to 11.5 points.

Thus, a favourable effect of HBOT on GCS improvement was noted, with the statistical significance of $p<0.05$. The diagnostic parameters of GOS, on the other hand, were examined three times in both groups.

The end results were evaluated and analysed immediately after HBOT intervention, as well as three and six months after TBI. In the evaluation conducted after three months, despite a certain improvement observed in the researched group in relation to the control group, the end results were not statistically significant. In the sixth month, 12 patients from the HBOT group and 9 patients from the group without an intervention indicated an improvement; however, the differences were not statistically significant with In the retrospective analysis performed by Sahni et al. [44] a hypothesis was adopted stating that HBOT as a method supporting standard treatment in patients with TBI may improve the end points. The research included 40 patients with severe TBI, with 10% of them < 1 month from the injury, 65% between 1-6 months, and 25% 6 months or more from the time of injury. The researched group (n=20) was provided with standard care and HBOT treatment of 1.5. ATA for 60 min, once a day, for 30 days, whereas the control group (n=20) received only standard care. The age difference among 80% of patients reached 15-50 years, and 65-80% of them were men. Both groups were subjected to diagnostic examinations with the use of the Disability Rating Scale (DRS), GCS and Rancho Los Amigos Scale (RLAS). The analysis of the end results of the DRS indicated maximum improvement and effectiveness in the researched group (before 45%, after 5%) as compared with the control group (before 45%, after 25%) among patients in a vegetative state.

The mean DRS values decreased from 23.75% to 18.85% for the researched group, whereas in the control group the result was reduced from 23.4% to 21.65%. In the RLAS in the group subjected to HBOT before treatment commencement, 95% of patients obtained the exact result of 3 points or less. The end result changed to 35% after the intervention.

The control group had a similar result before the treatment, 90%, however its results after the received care were significantly lower - 60%. The authors of the study analysed the therapeutic efficacy in both groups based on the time from the TBI. It was observed that in the researched groups the maximum improvement was accomplished with HBOT being implemented within 1-6 months (DRS: 23.3 – 17.25, RLAS: 2.08-4.00) as opposed to < 1 month (DRS: 26.0 – 22.4, RLAS: 1.6 – 3.4) and 6 months or more (DRS: 22.6 - 19.0, RLAS: 2.3 - 2.6).

In the control group, a significant improvement was also noted among patients 1-6 months after their incident. However, an analysis of the patients of the same category in the HBOT

group showed a more positive therapeutic effect as compared to the control group. Namely, a significant increase in the mean values of RLAS were noted in the researched group from 2.08 to 4.00, as compared with the control group's values amounting from 1.69 to2.69, and a decrease in the DRS results in the researched group from 23.3 to 17.25 in relation to the change in the values in the control group from 23.38 to 21.92.

A study by Boussi-Gross et al. [45] may be perceived as one of the most current and reliable scientific reports revealing statistically significant results of HBOT. This prospective, randomised analysis involved 56 patients after moderate TBI and a long-lasting post-concussion syndrome (PCS), being 1-5 years from the incident. The patients in the researched groups with HBOT intervention (n=36) with the dose of 1.5 ATA for 60 min, once a day, for 40 days were evaluated twice, before and after the treatment. Three analyses were carried out for the control group: before and after 2 months from the standard treatment (n=31) as well as after another 2 months from the implementation of HBOT with an identical dosage as in the researched group (n=24).

The applied *Mindstreams* test used in the cognitive evaluation measured the Quality of Life (QOL) verified with *EQ-5D* and *EQ-VAS*, whereas changes in brain activity were examined with Single Photon Emission Computed Tomography (SPECT). In the researched group the cognitive indexes showed an increase with regard to Information Processing Speed by 4.20 (p<0.0001), Attention by 3.26 (p<0.005), Memory by 4.13 (p<0.0005) and Executive Functions by 3.72 (p<0.0005). No significant improvement was observed in the control group: Information Processing Speed 0.53 (p=0.298), Attention 0.33 (p=0.368), Memory 0.74 (p=0.223) and Executive Functions 0.54 (p= 0.295). However, the control group that was subjected to HBOT after the lapse of 2 months also presented satisfactory results: Information Processing Speed 1.98 (p<0.05), Attention 2.29 (p<0.05), Memory 3.21 (p<0.005), Executive Functions 2.26 (p<0.05). The EQ-5D index in the researched group was improved by 7.41 ($p<0.0001$). A similar result of 6.17 (p<0.0001) was obtained by the control group after HBOT. As expected, there was no significant improvement in the pre-HBOT control group 2.60 (p<0.01).

The end results for EQ-VAS were also significantly improved after HBOT, both in the researched group 4.86 (p<0.0001) and the control group after HBOT 4.79 (p<0.0001), whereas no significant improvement was achieved in the pre-HBOT control group 0.32 (p<0.373). Thus, after an analysis of results we may conclude that the examination indicated facilitation of cognitive functions and QOL in both groups subjected to HBOT. However, no such changes were observed in the control group. Additionally, SPECT revealed an increased brain activity, thus indicating good compliance with an improvement of cognitive functions.

A similar researched was undertaken by Walker et al. [46] whose aim consisted in an effect analysis one week after HBOT intervention on the disturbed psychomotor and cognitive functions among soldiers after moderate TBI with PCS lasting 3-36 months. In a randomised double blind study 60 subjects were assigned to three groups. Two of them were subjected to HBOT, one with the dose of 2.0 ATA for 60 min, once a day, for 40 days, and the second with 1.5 ATA for 60 min, once a day, for 40 days. The third group was administered compressed air. The end results were measured with methods including computerized posturography (balance), grooved pegboard (fine motor speed/dexterity), and multiple neuropsychological tests of cognitive performance, collected pre-intervention and 1-week post-intervention.

The thus obtained values indicated an insufficient level of significance of 5% in all of the applied diagnostic methods. The exposure in both HBOT groups showed no favourable effects as compared with the control group. Wolf et al. [47] conducted a double blind randomised prospective study on 50 members of the military service with moderate TBI. The researched group (n=25) was subjected to HBOT of 1.5 ATA for 90 min, once a day, for 30 days, whereas the control group (n=25) was subjected to air exposures at 1.3

ATA for 90 min, once a day, for 30 days. The end results were measured with the Post-traumatic Stress Disorder Checklist - Military Version (PCL-M) and the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) before the intervention and 6 weeks after treatment completion. The PCL-M (t= -0.205, p = 0.84) and ImPACT (t= -0.943, p = 0.35) tests in the end showed no statistically significant differences between both groups. However, PCL-M and ImPACT indicated a significant improvement both in the researched (t = 3.90, p = 0.001) and the control group (t = 3.76, p = 0.001). The results may suggest that the implementation of HBOT with a given protocol had no effect on the symptoms occurring after a moderate TBI. Currently, there are two studies carried by Rockswold et al. [48,49], whose aim was to analyse the therapeutic efficacy of HBOT and Normobaric Hyperoxia (NBH). The experiment examined cellular metabolism in the brain with the help of the following parameters: mean brain tissue PO2; CBF; cerebral metabolic rate of oxygen (CMRO2); microdialysate lactate; microdialysate lactate/pyruvate (L/P) ratio; microdialysate glicerol. Intracranial pressure (ICP) was evaluated as oxygen toxicity was measured with the use of the following markers: ventricular colony stimulating factor (CSF) F2-isoprostane, bronchial alveolar lavage interleukin - 6 (BAL IL-6), BAL IL-8. In the first study, the evaluation was concerned with patients with severe TBI in an acute stadium 24 h from the incident. 69 patients with the mean value of GCS of 5.8 points were randomly assigned to three groups.

The first group (n=26) was treated with HBOT at 1.5 ATA for 60 min, once a day, for 3 days. The second group (n=21) was subjected to NBH with the exposure to 1.0 ATA for 3 hours, once a day, for 3 days. The third group, on the other hand, received standard medical care. In the course of the treatment the level of brain tissue PO2 in the group with HBOT (mean ± SEM, 223 ± 29 mm Hg) and the group with NBH (86 ± 12 mm Hg) was significantly elevated ($p<0.0001$) as opposed to the control group. Additionally, 6h from HBOT a significant increase was observed in CBF and CMRO2 ($p\leq 0.01$). After the treatment, the cerebrospinal fluid reduced lactate concentration both in the HBOT and NBH group ($p<0.05$). As a result of the applied therapy there was a reduction in microdialysis L/P ratio ($p<0.05$) in patients after HBOT and NBH. ICP proved to be much lower after HBOT and maintained its level until the following session (0.001) as compared with the control group.

The effect remained unchanged during 3 days of therapy. The parameters of the ventricular CSF F2-isoprostane, BAL IL-6, BAL IL-8, which were used to monitor toxicity potential did not increase. [48] In the second test, 42 patients with severe TBI were subjected to treatment within 24 h from the incident (mean GCS score 5.7). In the researched group (n=20) the HBOT/NBO combination was applied with HBOT of 1.5 ATA for the period of 1 hour, followed by NBO of 1.0 ATA for 3 hours, once a day, for 3 days. The control group (n=22) was subjected to standard treatment. In the researched group, during the treatment, the ($p=0,0003$) level of brain tissue PO2 was increased by 600% as compared with the control group ($p<0.0001$). On average the initial level of brain tissue PO2 was similar in both groups and amounted to 30 +/- 4 mmHg. During HBOT/NBO intervention, the mean level of brain tissue PO2 grew to 221 +/- 20 mmHg. In comparison with the control group the level of brain tissue PO2 in HBOT/NBO after intervention completion was higher even by 30% for a minimum of 2.5h ($p<0.0001$). In the course of treatment, and after the intervention, the microdialysate L/P ratios in the researched group was significantly decreased by 5% ($p=0.0078$) as compared with the control group. The levels of microdialysate glicerol were significantly lower in the researched group - by 14 % during the therapy ($p=0.0003$) and 12 hours from intervention completion ($p=0.0193$). The values of ICP in the HBOT/NBO were significantly lower than in the control group ($p<0.0003$) and were maintained at a low level until the next therapeutic session ($p<0.0006$). Patients with ICP higher than 15 mmHg before treatment experienced its greater decrease in the researched group as compared with the control group

($p<0.0001$). The levels of *CSF F2- isoprostane, BAL IL-6, BAL IL-8* were not statistically significant. Also, there was an absolute risk reduction (ARR=26%) in the researched group as compared with the control group ($p=0.048$) [49].

Tab. 2.

Summarised results of clinical examinations with the use of HBOT after TBI.

Research	Clinical research	Disease classification	Population	Intervention	Comparative intervention	End result measurement	Results for HBOT
Walker et al. (2013)	Randomised,	moderate TBI + post-concussion syndrome (PCS)/ 3-36 months from the incident	n= 61 TG1 n= 18 TG6 n= 61 CG	**TG1:** HBOT6.0 ATA 60 min. 1 per day for 40 days; **TG2:** HBOT 1.5 ATA 60 min. 1 per day for 40 days	**CG:** Air	Psychomotor Functions: *1. Grooved Pegboard Test (GPT)* *2. Sensory Organization Test (SOT)* Cognitive Functions (focus and executive functions): *1. D-KEFS LetterFluency* *2. Trails B* *3. Stroop Color-Word* *4. CPT-II Detectability Index* *5. PASAT 2.0* Cognitive functions (Memorising and operational memory): *1. WAIS III Working Memory Index* *2. CVLT Long-Delay Free Recall* *3. CVLT Index* *4. BVMT-R Delayed Recall* *5. BVMT-R Discrimination Index*	No significant improvement
Boussi-Gross et al. (2013)	Randomised; prospective	moderate TBI + post-concussion syndrome (PCS)/ 1-5 years from the incident	n= 45 TG1 n=64 TG6 n= 45 CG	**TG1**: HBOT 1.5 ATA 60 min. 1 per day for 40 days **TG2**: HBOT 1.5 ATA 60 min. 1 per day for 40 days	**CG1:** Standard treatment; **CG2:** no	1. *Mindstreams cognitive indices scores*: memorising, executive functions, focus, information processing speed. *2.EQ-5D questionnaire* *3. EQ- VAS questionnaire* 4. *SPECT*	↑ Memory (p<0.0005) ↑ Executive functions (p<0.0005) ↑ Focus (p<0.01) ↑ Information processing speed (p<0.0001) ↑ *EQ-5D for HBOT* (p<0.0001) ↑ *EQ-VAS for HBOT* (p<0.0001)
Rockswold et al. (2013)	Randomised; prospective	Severe TBI/ 64 h from the incident	n= 60 TG n= 66 CT	**TG:** combined HBOT/NBH 60 min. HBOT 1.5 ATA followed by NBH for 3 h of 100% FiO6 1.0 ATA	**CG:** Standard treatment	1. Scale (GOS) 6. Intracranial pressure (ICP) 3. *CSF F2-isoprostane* *4. Microdialysate L/P*	↑ GOS (p = 0.064) ↓ ICP (p<0.0001) ↓*CSF F2-isoprostane* (p =0.0696) ↓ *Microdialysate L/P* (p <0.0078)

cont. Tab. 2.

Sahni et al. (2012)	Retrospective,	severeTBI/ 10% < 1 month 65% = 1– 6 months 65% < 6 months after the incident	n = 60 TG n= 60 CG	**TG:** HBOT 1.5 ATA 60 min. 1 per day for 30 days	**CG:** Standard treatment	1. *Disability Rating Scale* (DRS) 6. Glasgow Scale (GCS) 3. *Rancho Los Amigos Scale* (RLAS)	↓ DRS (63.3 - 17.65) ↑ RLAS (6.08 – 4.00)
Wolf et al. (2012)	Randomised; prospective	Moderate TBI	n = 65 TG n = 65 CT	**TG:** HBOT 1.5 ATA 90 min. 1 per day for 30 days	**CG:** Air 1.3 ATA 90 min. per day for 30 days	1. *PosttraumaticStressDisorderChecklist - Military Version* (PCL-M) 6. *Immediate Post-Concussion Assessment and Cognitive Test* (ImPACT)	No significant improvement
Rockswold et al. (2010)	Randomised; prospective	Severe TBI/ 64 - 48h from the incident	n = 66 TG1 n = 61 TG6 n = 66 CG	**TG1**: HBOT 1.5 ATA 60 min. 1 per day for 3 days **TG2:** NBH 1 ATA 3 h 100% FiO6 1 per day for 3 days	**CG:** Standard treatment	1. Cerebral blood flow (CBF) 6. Cerebral metabolism rate of oxygen (CMRO6) 3. Intracranial pressure (ICP) *4. CSF lactate* *5. CSF F2-isoprostane etc.*	↑CBF ($p \leq 0.01$) ↑CMRO6 ($p \leq 0.01$) ↓ICP ($p < 0.001$) ↓CSF lactate ($p = 0.045$) No significant improvement: *F2-isoprostane levels,* *microdialy sate glycero*l, BAL inflammation markers
Lin et al. (2008)	Prospective; cohort	Severe TBI/ 67.5 +/- 5.8 days prior inclusion	n = 66 TG n = 66 CG	**TG:** HBOT 6.0 ATA 90 min. 1 per day for 60 days	**CG:** Standard treatment	1. Glasgow Scale (GCS) 6. Glasgow Outcome Scale (GOS)	↑ GCS ($p < 0.05$) 0.05)

DISCUSSION

Preclinical tests revealed a repeatable therapeutic effect. In many of them the exponents of an inflammatory state, which are of crucial importance in late TBI outcomes, were precisely analysed. Due to the applied combination of behavioural tests and computerised neuroimaging, the Xiao-Er Wer test showed not only a decrease of an oedema but also an improvement in locomotor functions and a growth in the muscle strength [39-42]. Preclinical tests may have a direct impact on the dynamics of development of clinical research, and, in the years to come years, on a broader application of HBOT. A particularly important aspect of HBOT application in TBI consists in working out procedure protocols with the specification of therapeutic dosage, therapy time and other related elements.

The end results of the clinical research appeared to be somewhat contradictory. The concept of HBOT implementation as a supporting method in treating TBI still raises certain controversies in medical environments. Two studies by Rockswold et al. [48,49] were carried out on patients after severe TBI after 24 - 48 h from the incident. One of them applied only HBOT, whereas the other HBOT was combined with NBH. In both cases there was a visible facilitation of metabolic processes in the brain, a reduction in intracranial pressure and a lack of an increase in the markers related to oxygen toxicity. The remaining tests evaluated the therapeutic efficacy of HBOT among patients in a later stadium. HBOT was provided as a rehabilitative treatment, facilitating the functional and cognitive activities. Lin et al. [43] in HBOT protocol applied the dose of 2.0 ATA among patients with severe TBI being on average 27.5 +/- 5.8 days from the injury. The author's conclusion was that HBOT could be beneficial in treating TBI. Sahni et al. [44] also made similar conclusions when treating patients with severe TBI being on average 1-6 months from the injury with HBOT of 1.5 ATA. In the study conducted by Walker et al. [46], which included patients after moderate and/or PCS maintained for 3-36 months, an insufficient significance level was observed. In consequence, a thesis was written concerned with the invalidity of using HBOT of 1.5 ATA and 2.0 ATA in treating cognitive and psychomotor deficits resulting from the researched conditions.

A similar therapeutic result of HBOT of 1.5 ATA was obtained by Wolf et al. [47].

On the other hand, different and highly statistically significant end results were obtained by Boussi-Gross et al. [45] in a study on patients 1-5 years from a moderate TBI as well as and/or with PCS. A prospective randomised study evaluated the disturbed cognitive functions and QOL after an intervention with HBOT of 1.5 ATA. Efrati et al. [50] suggested that it was impossible to determine and evaluate the effects of hyperbaric therapy when applying HBOT in an acute and early stadium after TBI, as at this stage spontaneous brain tissue regeneration is also active. Moreover, an increased level of oxygen may decelerate natural regeneration processes in certain people or induce toxicity. On the other hand, a patient in a chronic stadium shows neurological stability with little probability of an occurrence of spontaneous changes that are not related to HBOT.

According to the author, this theory could explain the negative results obtained in the studies using HBOT in an early phase after a stroke [51,52,53,54,55]. The discussed studies were characterised by diversified working protocols. We may presume that factors such as: the stadium of TBI, level of intensification of TBI, HBOT dose, time and number of compressions could affect the outcome of the research. Therefore, in order to resolve the above dispute it is recommended to conduct further prospective, randomised and multi-center research. New reliable scientific reports would enrich our knowledge on this subject and could help in drafting a universal working protocol regarding HBOT application for TBI.

CONCLUSIONS

Preclinical studies indicated a considerable medical potential of HBOT. An analysis of clinical studies, on the other hand, revealed equivocal and somewhat contradictory final results. It is necessary to conduct further prospective randomised research that could help to evaluate the real therapeutic effect of HBOT in patients after TBI.

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