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THE EFFECT OF HYPERBARIC OXYGEN THERAPY ON THE NERVOUS SYSTEM. SYSTEMATIC REVIEW

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) is found among the interests of researchers who seek new methods of treatment of diseases of the nervous system. An increase of the partial pressure of oxygen in arterial blood within the appropriate range leads to numerous changes in the cells of the brain tissue. In this paper we analyse the results of selected articles describing HBOT used on pathologies of the nervous system such as stroke, autism, multiple sclerosis and cerebral palsy as well as in the course of research on animal models. The results are promising, although some studies struggled with numerous methodological problems and differences in the applied protocols, which resulted in conflicting results in individual interventions. In consequence, the need for further studies in randomised control trials and determination of the protocol by an international group of researchers dedicated to the use of HBOT was emphasised.
Key words: cognitive functioning, hyperbaric chamber, brain, hyperbaric oxygen therapy.

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INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is characterised by an inhalation of an increased amount of oxygen in a hyperbaric chamber in pressurised conditions, which exceeds the pressure of the atmosphere defined as 1 absolute atmosphere (1 ATA) [1, 2]. The scope of pressures used in HBOT oscillates between 1.5 ATA and 3 ATA, whereas therapy duration is set between 30 and 120 minutes [2, 3, 4, 5, 6]. Inhaling oxygen at 3 ATA increases the partial pressure of oxygen in the blood to 200 kPa and more, which leads to an increase in the product of oxygen concentration in arterial blood from 6.6 to 6.8 ml (O_2/100ml) [7].

In normal circumstances O_2 is transported in the blood only with haemoglobin in red blood cells, which constitutes 98% of blood saturated with O_2 [8]. In the conditions of normal atmospheric pressure (1 ATA), red blood cells make up only 45% of the blood whereas the plasma transports very small quantities of O_2 [8]. What is crucial in the case of HBOT, when the pressure rises to 3 ATA, the amount of O_2 delivered with the blood increases from 10 to 15 times above the norm, which gives us a quantity sufficient for life support even in the case of absence of haemoglobin [8].

Even a slight increase in the partial pressure, such as 1.05 ATM at the depth of 402 below sea level may induce observable physiological changes [9].

It is possible to distinguish several factors that play a major role in treatments based on HBOT [10]. These include: neutrophils, metaloproteinases, caspases and hypoxia-induced factor (HiF-1) [10]. Since 1 cm^3 of a regular nervous tissue contains ca. 1 km of blood vessels, a sufficient oxygen supply is absolutely necessary to repair damaged regions [11].

The effect of HBOT on neurons may occur indirectly through neuroglial cells and astrocytes [12].

MATERIAL AND METHODS

The following electronic full-text bibliographic databases were searched by entering the following key words hyperbaric oxygen therapy, neuropsychological tests, brain: EBSCO host Web, Wiley Online Library, Springer Link, Science Direct and Medline.

The inclusion criteria allowed the authors to consider research conducted on animal models, and moreover the selected studies could use different HBOT protocols; they used cognitive functions tests and measured the therapeutic effectiveness of HBOT on patients with pathologies in the nervous system.

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 1990-2015. The exclusion criteria concerned research 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, control group and end point.

RESULTS

1. HBOT safety

HBOT safety was tested in all age groups, including new-borns [13, 14, 15] and pregnant women [16, 17]. The side effects of HBOT were noted, in particular with regard to the use of high pressure (>3 ATA) and in the case of a long duration [25].

It was indicated that the use of HBOT at the pressure of 4.96 ATA for the period of one hour [19] may be neurotoxic. Oxygen shock caused by the use of a pressure higher than 4 ATA induces a lipid peroxidation process [20, 21], however it does not cause such effects in the conditions of a pressure lower than 3 ATA [22, 23].

2. HBOT as treatment for selected pathologies of the nervous system

A lower level of oxygen not only leads to a reduced neuron activity but also disables creation of new synaptic connections and prevents angiogenesis [24]. HBOT can indirectly initiate repair of blood vessels, improve cerebral circulation and the ability of vascular endothelium to nitrogen synthesis or axon regeneration, stimulate their growth, strengthen the integrity of the blood-brain barrier and reduce inflammatory states as well as cerebral oedema [2, 12, 25].

HBOT activity prevents the widening of capillary vessels within the ischaemic tissue which minimises the oedema, which also results in the reduction of intracranial pressure [5, 6].

2.1. Stroke

It is worth noting that stroke and cerebrocranial injury may in consequence intensify depolarisation of mitochondrial membranes and increase their permeability, which reduces the energy productivity and elevates the level of reactive forms of oxygen [18]. HBOT may decrease permeability of mitochondrial membranes and has the potential to reverse this anomaly [2].

Assuming that the main factor prohibiting recovery of the efficiency of nervous tissue following an ischaemic episode is the absence of reperfusion, the oxygen delivered by use of HBOT may be conducive to the reperfusion of an ischaemic area due to a greater pressure gradient, even with the presence of a reduced blood flow in the brain [26]. What is interesting, through the contraction of cerebral vessels, HBOT induces a reduction in the blood flow in the brain by 20-30% [27, 28], which is connected with a significantly decreased amount of supplied oxygen and may result in the occurrence of spontaneous hyperventilation attributed to regional cerebral acidosis [29].

At this point it is worth providing a description of retrospective analysis of changes in the functioning of memory and the connected brain activity in 91 stroke patients [30]. The study encompassed at least 40 HBOT sessions and two cognitive functions appraisals (before and after HBOT). Memory assessment was performed with the use of a collection of computerised cognitive tests "Neurotrax", previously known as "Mind-Streams" [30], of which the tests on immediate and reference verbal and non-verbal memory were used.

Moreover, the analysis took into account the total result of the aforementioned four tests. A more detailed description of the applied tests can be found separately [30, 31]. Brain activity analyses were performed with the use of single photon emission computed tomography (SPECT).

Patients with noted 'clinical improvement', particularly those with improved results in reference memory tests also indicated a relatively higher cortex activation as compared with those in whom the 'clinical improvement' was not observed. Before the intervention, the patients were tested with the use of a neuroimaging technique to determine the lesion area defined as the penumbra zone. It is an area characterised by critically reduced cerebral flow and synaptic activity with preserved structural integrity.

The authors [30] see the specified areas as the key to improve the condition of post-stroke patients, however also emphasise that the use of HBOT with the aim to regenerate the penumbra zone requires further research. Nonetheless, it is worth noting that the authors [42] did not include a control group in the study and provided a rather perfunctory description of their understanding of a 'clinical improvement'.

In certain patients an increased oxygen level may inhibit natural regeneration or even induce toxicity. The researchers [11] argue that this may explain the contradictory results of research with the use of HBOT in patients immediately following a cerebral episode [32-36].

2.2. Autism

One of the directions of studies conducted with the use of HBOT that experiences methodological and qualitative problems is concerned with treatment of autistic children [37, 38]. In 2012 a systematic review was published [37] describing the results of research with HBOT for the purpose of improvement in the condition of children with autism.

The author [37] points out that the evaluation of HBOT results is often performed with the use of tests measuring e.g. social or communicational problems of participants which, according to the author, lack objectivity. Moreover, the author highlights [37] that further studies should take into account the fact that over half of the patients with developmental disorders also suffer from attention deficit hyperactivity disorder.

2.3. Multiple sclerosis

In a recently published review article concerned with the treatment of multiple sclerosis patients [39] the author describes the findings made in 1962 [40]. The researchers determined the location of nearly one thousand six hundred macroscopic lamellae and found it peculiar that they were located in peripheral zones of the main cerebral arteries.

The border zones between the main arteries are characterised by a reduced pressure of the oxygen present. Imaging performed with the use of magnetic resonance on 1249 multiple sclerosis patients indicated a high level damage in the above-mentioned areas [41]. Meta-analysis of neuroimaging tests allowed to make an observation that the cortex in multiple sclerosis patients is exposed to higher atrophy along the borders of arterial vasculature as compared with other areas. [42].

When used as a therapy of multiple sclerosis, HBOT is seen to create a temporary improement in the sufeffers symptoms, however thus far no long-term results have been confirmed [43, 44]. The ineffectiveness of HBOT is explained by an increased oxidative stress which, according to some authors, may occur in such conditions [45].

2.4. Cerebral palsy

The study of 2001 was conducted on 111 cerebral palsy patients aged between 3 and 12 years [46]. The participants were randomly assigned to a group staying in a hyperbaric chamber for 60 minutes (n=57), at a pressure of 1.75 ATA, with 100% oxygen concentration, or to a *sham treatment group* with the use of 1.3 ATA (the smallest pressure change sensed by humans) [17].

Both groups were subjected to 40 sessions lasting one hour. The neuropsychological tests performed on 75 patients included: a computer version of Corsi blocks, Word span and a Test of Variables of Attention (TOVA) [46]. Research results showed an improvement in time in both groups in general results of working memory and attention tests, however no such improvement was noted with regard to response time in attention measurement tests.

The authors [46], as well as others [17] determined that the use of HBOT with the applied pressure of 1.3 ATA may induce significant physiological changes in patients, hence the use of such an intervention in the *sham treatment group* serves no purpose [17]. On the one hand, a pressure increase to 1.3 ATA is the smallest increase that the patients are capable of sensing, thus it would be an ideal type of intervention for studies with the use of HBOT if such a pressure rise did not possibly induce an over 50% oxygenation increase in tissues [17], a situation which could suggest that therapies using the pressures of 1.75 ATA and 1.3 ATA can be equally effective [46].

An additional source of conclusions from the above studies [46] is found in the correspondence of other researchers with the authors [46] published in *The Lancet* [47]; these suggested that each study measuring the effects of therapy among patients with brain damage should be enriched with SPECT in order to ensure maximum objectivity.

Furthermore, the authors [46] emphasised that despite the convincing evidence from scientific research on HBOT effectiveness in children with cerebral palsy it was not possible to find a link between the applied therapy, the results of neuroimaging tests and a clinical improvement in patients [47].

3. Methodological problems during clinical research

The debate on HBOT mainly focuses on matters related to the control group and the least effective dose, i.e. the pressure which does not evoke any physiological effects in the nervous system [1, 3, 4]. A recently published article [48] presents several issues connected with drawing conclusions on the basis of the results of studies using HBOT.

Among other things, the paper describes the problem connect with a sham treatment group being exposed to 1.2 ATA, which results in a pressure increase of 20%, thus, theoretically, the oxygen level in the blood should increase by 30% as compared to the level in regular pressure conditions [48].

Some research reports describe cases where even slight pressure increases in various tissues, including cerebral tissues, sufficed for the changes to occur [46]. A deferral upon which the estimation of the HBOT effect was performed is significantly different in particular studies, which may explain the inconsistency in the

obtained results [48].

The evaluation was carried out 3 days [49], 1 week [3], 1 month [50], 6 weeks [4], 2 months [51], 3 months [52, 53] after the last exposure in the chamber. What is more, the timing of the initiation of HBOT therapy in patients with mild post-traumatic brain damage varies among particular studies and falls between three months and three years after the first trauma [3, 4, 49-53].

The pilot studies conducted in 2003 deserve a closer look [34]. The conclusions provided by the authors' state that the research was based on a protocol using HBOT at a pressure of 2.5 ATM for 60 minutes, which, although being safe and feasible, does not seem to be effective as a therapy in patients with severe ischemic stroke.

The obtained results were so disappointing for the authors that they aborted a larger clinical trial and stopped at the pilot study [34].

Other researchers also confined themselves to pilot research [32]. 39 patients with ischemic stroke participated in the studies, however the authors [32] did not note a significant improvement in the course of HBOT, moreover, certain problems occurred in patients' following the therapy schedule and 4 months into the research an error in the patient randomisation process was noted. The study was thus aborted without plans of its reopening [32].

4. Animal models

One of the studies, analysing the impact of HBOT with the use of animal models and cell cultures, involved the use of HBOT for a period of 1 hour at a pressure of 2.5 ATA and 100% oxygen supply, for 5 consecutive days in the case of an animal model, or for 2 hours at 3.5 ATA in the case of cortical neuron culture [54].

The researchers managed to cause focal cerebral ischemia in one of the animal groups. The Western-Blot test was used to measure the level of SirT1 proteins in ischemic penumbra zones before an ischemic episode,1, 3, 6, 12 and 24 hours after the reperfusion [54]. SirT1 proteins became the centre of the researchers' interest due to, among other things, their activity connected with an increasing cellular survival rate in stress conditions described in the available literature [55].

The analysis showed that SirT1 proteins play the major role in inhibiting apoptosis during HBOT in an animal model testing cerebral ischemia. The researchers suggest that their findings have revealed the mechanism underlying the neuroprotective effects of HBOT [54].

Research results from 2001 [56] inform us that HBOT interventions reduced the levels of glucose, pyruvate and glutamate from the penumbra zone to levels comparable to those prior to the occlusion [56]. What is more, it was suggested [57] that the reduced level of dopamine may be partially responsible for the neuroprotective mechanism of HBOT in the cases of focal brain ischemia.

In other studies [58] 64 rats with unilateral lesions in the cerebral cortex were tested with the use of the Morris water maze between 31 and 33 days following lesion occurrence. Next, they were divided into 3 groups: without an intervention (n=22), with the use of HBOT (n=19) and a sham group (n=23) [58]. The HBOT group

received 80 therapy units for 7 days a week with the pressure of 1.5 ATA applied for 90 minutes [58]. The density of blood vessels was examined in the hippocampi with the use of diaminobenzidine (DAB). HBOT caused a significant increase in the density of blood vessels in the damaged hippocampi, which was related to a statistically significant improvement in the results obtained in the Morris water maze [58].

Other studies were based on an animal model used for global ischemic stroke [59]. The protocol of an intervention group involved the use of HBOT an hour after the occurrence of an ischemic episode.

The results indicated a reduced quantity of dead neurons in the hippocampus regions in the intervention group [59]. It was demonstrated that the application of HBOT (3 ATA for 2 hours) an hour after a brain episode prevented death of a significant number of neurons in the cerebral cortex and CA1 region of the hippocampus.

The study used Nissl staining 96 hours following a brain episode [59].

DISCUSSION

The use of HBOT is considered safe if the pressure is maintenance below 3 ATA and a proper intervention time is allowed. Interventions assessing the effect of this method in stroke patients are fundamentally different regarding the methodology in use, which may be the reason for obtaining conflicting research results.

In the case of HBOT application in children, the problem could rest in low level objectivity of result measuring tests in such categories as social and communication skills, as well as the frequent coexistence of other health conditions in the examined patients.

Studies seeing HBOT as therapy addressed to multiple sclerosis patients did not demonstrate long-term positive changes.

The analysis of studies concerned with hyperbaric therapy of patients with cerebral palsy revealed a whole spectrum of methodological issues. Moreover, the authors point out the fact that despite the reasons provided in scientific literature on HBOT efficacy, in the case of this condition, it is not possible to draw conclusions on the causality between the use of HBOT and an improvement in neuroimaging results, as well as other tests aimed at evaluating therapy results.

The research conducted on animal models have expanded the knowledge on HBOT mechanisms, as well as revealed statistically significant correlations between positive changes detected with neuroimaging techniques and cognitive test results.

CONCLUSIONS

HBOT is a therapy inducing a broad spectrum of changes in the functioning of the nervous tissue that theoretically can be conducive to a health improvement in patients with conditions related to the nervous system.

Before HBOT is implemented as a permanent element of therapeutic programmes of clinical centres there is a need to conduct a larger number of randomised studies on patients with nervous system diseases.

It is important that the community of researchers undertaking research on patients with the use of hyperbaric chambers determine a protocol that contains instructions related to an intervention performed on a sham therapy group.

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