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ADVERSE EVENTS DURING HYPERBARIC OXYGEN THERAPY – LITERATURE REVIEW

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ABSTRACT

As any other therapy method, hiperbaric oxygen therapy is connected with the risk of complications. The article is a review of the results of research on adverse events of hyperbaric oxygen therapy. The most common are: borotrauma of the middle ear, paranasal sinuses or lungs, oxygen toxicity can be pulmonary, ocular in extreme cases leading to cataracts, claustrophobia, pulmonary edema or hypoglycaemia. Research has shown that these events occur in the presence of high oxygen concentration or high pressure. Depending on the severity of complications, they are short-term not causing discontinuation of therapy or long-term excluding continuation of treatment. However adverse events connected with oxygen therapy are not common and are usually mild. This confirms that HBOT is an effective and safe method of treating decompression sickness, carbon monoxide poisoning, and the treatment of chronic wounds, delayed radiation injuries or necrotic soft tissue infections.
Keywords: Hiperbaric oxygen therapy, HBOT, safety, complications of oxygen therapy.

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INTRODUCTION

HBOT is approved by The Undersea and Hyperbaric Medical Society (UHMS) and European Committee for Hyperbaric Medicine (ECHM) for the treatment of: iatrogenic gas embolism (IGE), decompression sickness (DCS), carbon monoxide or cyanide poisoning, smoke inhalation damage, necrotic soft tissue infections, crush injuries, pressure ischaemic syndromes, acute post-traumatic peripheral ischaemia, refractory osteitis, and bone marrow, damaged flaps or skin grafts, and to enhance the healing of selected wounds [1]. HBOT is more and more often used in different diseases [2]. HBOT can be safely used in the ICU and improve the prognosis of certain pathologies. The increase in tissue oxygen pressure causes a number of physiological effects, such as an increase in arterial oxygen content, the vascular effects of hyperoxic vasoconstriction, the most important of which is the reduction of oedema and the fight against infection and healing [3].

HBOT is generally a safe and well-tolerated method, but there may occur some complications during the therapy [4]. Numerous studies have shown more or less serious adverse effects of HBO treatment due to high blood pressure or high oxygen levels. Increased pressure can result in a middle ear injury or pulmonary barotrauma. High oxygen levels can damage the central nervous system, lungs, or lead to eye complications [5]. Complications occurring during treatment with hyperbaric oxygen, apart from the division into toxic complications of oxygen and complications of the compression process, can be divided into: short-term, which lead to premature termination of a given compression (such as: ear pain or sinus pain), but do not exclude continuation of the therapy, and complications that preclude further ventricular therapy (e.g. cerebral or ocular) [6]. The main side effects of HBOT are barotrauma and claustrophobia. Barotrauma is not uncommon and may affect the middle ear (MEB), teeth, sinuses, and lungs [1]. Less often convulsions related to oxygen toxicity and hypoglycaemia were observed. Pulmonary barotrauma has been reported extremely rarely [7]. Other disadvantages of HBOT are: limited availability of hyperbaric centres, lack of access to immediate medical care in hyperbaric chambers and transporting patients over long distances [8].

People who require urgent HBOT treatment are generally in critical condition, so in addition to complications directly related to HBOT, they may experience various unexpected events. Emergency HBOT is recommended within 24 hours after exposure to CO poisoning. In many cases, HBOT is thus initiated before the patient's state of health is fully known. Acute HBOT should be performed not in a single-site chamber, but in a multi-site chamber, where trained medical personnel accompanies the patient and can immediately detect changes in his condition [9].

In most papers HBOT is considered safe. Only a few studies report a higher number of complications with the use of hyperbaric oxygen therapy [6].

SIDE EFFECTS OF HBOT

MIDDLE EAR BAROTRAUMA

Of all the side effects of HBOT, MEB is the most common (around 2%). The MEB in patient reports is characterized by ear discomfort, a blockage or feeling of fullness in the ear, and difficulty equalizing pressure in the ear. Symptoms of MEB can include, in addition to the feeling of pressure in the ears, earache, headache, dizziness, tinnitus, and hearing loss [4,10,11]. In the absence of care, swelling can develop in the middle ear, and in rare cases, rupture of the eardrum. When barotrauma affects the inner ear, the inner ear function may be impaired, causing dizziness and sensorineural hearing loss [10]. MEB is most often classified using the TEED scale (0 - for symptoms without otological signs of injury, 1 - indentation of the tympanic membrane, 2 - cavity of the tympanic membrane and slight haemorrhage, 3 - large eardrum haemorrhage, 4 - free blood in the middle ear, as evidenced by a bluish color and bulge, 5 - perforation of the eardrum) [4,10]. The vast majority of MEB cases (84%) were TEED 1 or TEED 2 with no episodes of rupture [10]. The discomfort level in an ear in MEB is assessed in the scale from 0 (lack of discomfort) to 10 (maximum discomfort). A higher score indicates a higher level of discomfort during HBOT. The results are measured at the start of the study before the first HBOT, after the first 5 consecutive HBOT, and after every 10 HBOT until the twentieth HBOT. When symptoms of MEB occur, the patient must undergo an otoscopic examination to diagnose and classify the extent of the injury [4]. More than a half of the otological symptoms associated with HBOT occur during the first chamber session. Of these, otalgia is the most common complaint of patients receiving HBOT.

MEB occurs most often when people during HBOT are unable to equalize the pressure gradient between the middle ear and the external environment. It is often the result of Eustachian tube (ET) malfunction due to birth defects, anatomical limitations, inflammation, or other pathological changes. People with limited ability to open the Eustachian tube, such as children, coma patients and those assisted by mechanical ventilation, may not balance the pressure during HBOT. HBOT-induced MEB may be caused not only by ET failure, but also by middle ear mucosa hyperaemia [11].

Only with an appropriate evaluation of the MEB can healthcare professionals decide whether treatment is necessary. It can take the form of extended follow-up education, medical intervention, or a surgical intervention such as a myringotomy and placement of a ventilation tube. Methods of preventing HBOT-related MEB include the Valsalva and Toynbee maneuver to open the Eustachian tubes and facilitate pressure equalization, the use of nasal decongestants to reduce middle ear congestion and swelling, and prophylactic myringotomy or tympanostomy tube placement [4].The reporting rate of MEB in patients undergoing HBOT varies significantly, ranging from 2% to 84% in non-intubated patients and over 94% in patients with a tube. The varied frequency range is due to different criteria for determining MEB, differences in the patient population, and differences in instructing the patient about pressure equalization in the middle ear. The occurrence of MEB depends on the rate of compression. Research has shown that a high

compression rate (4.1 psi / min) increased the risk of MEB. In their work Heyboer et al. suggested that a very followed. Risk factors for oxygen toxicity in HBOT treatment: increased treatment pressure (2 vs 2.4 / 2.5 vs 2.8 ATA), brain tumour / radioactive necrosis of brain soft tissues, carbon monoxide poisoning, hypoglycaemia and hyperthyroidism [10]. The cerebral form of acute oxygen poisoning, known as the Paul Bert effect, can occur when the partial pressure of oxygen (ppO2) is up to 180 kPa [1].

PULMONARY OXYGEN TOXICITY

Continuous exposure of the lungs to elevated levels of oxygen at hyperbaric atmospheric pressure leads to severe toxic effects. Pulmonary oxygen toxicity has two overlapping phases: the acute exudate phase and the subacute proliferative phase. In the exudate phase pulmonary changes include: interstitial and alveolar oedema, intra-vesical haemorrhage, fibrinous exudate, vitreous oedema, and destruction of endothelial cells of capillaries and type I alveolar epithelial cells. The proliferative phase is characterized by interstitial fibrosis, fibroblast proliferation, and proliferation of type II alveolar epithelial cells. The frequency and volume of inhalations and exhalations are reduced and the diffusion capacity of CO2 is reduced. Gradual reduction in vital capacity occurs. The rate of onset of pulmonary oxygen toxicity correlates with pO2 and exposure time. Oxygen toxicity most often occurs after 12–16 hours. at 1.0 ATA, 8-14 hours at 1.5 ATA, and 3-6 hours. at 2.0 ATA. Symptoms appear even earlier at 2.5 and 3.0 ATA, but are milder because the exposure time is shorter. Symptoms of pulmonary oxygen toxicity initially appear as mild sub-sternal discomfort. Persistent oxygen exposure results in chest tightness, extensive pleural chest pain, coughing, and shortness of breath. After the end of exposure symptoms improve in the first few hours and completely disappear within 1-3 days. Oxygen toxicity in the lungs can be avoided by supplying the right amount of oxygen. Subjects exposed to hyperoxia at 0.55 ATA for 7 days showed no signs of pulmonary toxicity. Exposure to 0.3 ATA for 30 days also resulted in no toxicity [10].

OPHTHALMIC OXYGEN TOXICITY

Increased partial pressure of oxygen can harm many tissues, including the eye. Duration of exposure, PO2, and many other variables (e.g., methods of oxygen delivery, age of individuals, presence of undiagnosed co-morbidities) can influence the development of ocular symptoms of oxygen toxicity. Older people may develop cataracts, while young people may develop extra-lens fibroplasia. Hyperoxic myopia is one of the most common eye side effects.

Progressive myopia is the result of repeated treatments with HBOT. The rate of this change reported in the literature is 0.25 dioptres per week and is sustained throughout treatment. Myopia is reported in 25–100% of patients undergoing HBOT for several weeks at a pressure of 2.0 ATA and more. The exact mechanisms behind the onset of myopia are not fully understood. Careful ophthalmological examination prior to initiating HBOT is essential, especially in patients who will undergo an extended course of treatment. The myopia developed during HBOT is reversible after the end of the treatment. Recovery from baseline usually occurs within 3-6 weeks, but can take as long as 6-12 months. HBOT leads to an increase in pO2 and ROS concentration in the blood and tissues, including the stroma of the cornea, which can lead to the formation of cataracts. Cataracts develop only after prolonged exposure to hyperbaric oxygen, usually 150 treatments or more. The exact mechanism of cataract formation with HBOT is not known. The oxidative damage to the lens protein plays a key role in long-term exposure to HBOT [10].

CLAUSTROPHOBIA

Claustrophobia may occur at patients who are conscious, especially in one-place chambers [1]. About 2% of the general patient population may have some degree of anxiety about occlusion, even in multi-place chambers. Restlessness in one-place chambers is reported in 8 cases out of 10,000 procedures. Mild anxiety can be managed with sedation prior to procedures. Severe cases may require a referral to a psychiatrist or psychologist for cognitive behavioural therapy, relaxation exercises, or long drug therapy. Signs of claustrophobia may include: sweating, increase in blood pressure, palpitations, hyperventilation, dizziness, choking, chest tightness, tremors, restlessness, headache or confusion [10]. Some people are unable to continue and complete their treatment. Treatment completion rates can be improved by better communicating with the patient, identifying people at risk of claustrophobia, and initiating appropriate preventive measures [7]. Educating patients, relaxing and coaching are effective ways to prevent claustrophobia episodes before HBOT [10].

PULMONARY OEDEMA

Patients with impaired left ventricular function during HBOT have a theoretical risk of pulmonary edema. Based on the available studies, Heyboer et al. showed that the risk is low. The incidence in two studies was 1 in 1,000 (0.1%) and 1 in 4,500 (0.02%).The aetiology of pulmonary oedema appears to be related to hyperbaric oxygenation, which induces increased systemic vascular resistance and decreased cardiac output. Pulmonary oedema can also occur as a result of increased pulmonary capillary pressure, damage to the heart muscle, use of endothelial NO by anaerobic free radicals, or an imbalance of cardiac output between the right and left hearts. In patients with congestive heart failure, echocardiography should be performed prior to HBOT and caution should be exercised. Patients should not be overloaded with fluids [10].

HYPOGLYCEMIA

HBOT affects residual insulin secretion in diabetics and increases the utilization of glucose in the brain. This can lead to hypoglycemia during HBOT in diabetic patients. The minimum serum glucose concentration before surgery ranges from as high as 150 mg / dl to as low as 100 mg / dl. Data collected by Heyboer et al. show that in diabetics, during HBOT, there is an average decrease in serum glucose levels, but with a large extent and a high percentage of patients who actually had an increase in serum glucose. There is no clear risk of any risk factors for developing hypoglycaemia. The results of the presented studies show

that only in a few cases the patients experienced symptomatic hypoglycaemia [10].

RESULTS OF THE RESEARCH REVIEW

1.

In their work Kobielska and Chrapusta presented all the adverse events observed over six years during the treatment of 1,981 patients (from 8 months to 97 years) in a hyperbaric multi-site chamber. All patients were trained on how to equalize the pressure in the ears. Any condition that contributed to the discontinuation of therapy was considered a complication, either before the end of the compression cycle or during a given compression (necessity of prior decompression of the patient). Each patient in the researched group had 1-60 sessions. In 185 patients, there were problems with the equalization of pressure in the ears during the compression. This qualified as an adverse reaction to the compression process. Unbalanced pressure in the ears was observed in 9.34% of patients. They were re-trained on how to equalize the pressure in the ears. Most of them have done it correctly in the following sessions. 39 patients out of 185 required consultation with a laryngologist. From the group of 39 patients, 18 were excluded from HBOT due to their disqualification by a laryngologist or for other, unspecified reasons. 21 patients continued therapy.

In the group of 1,981 treated patients, significant complications occurred in 17 patients (0.86%). The following complications were found:

- sudden myopia - 4 patients (0.2%);
- dyspnoea and chest pain - 3 patients (0.15%);
- sinus pain that made it impossible to conduct HBOT - 3 patients (0.15%);
- middle ear barotrauma - 2 patients (0.1%);
- convulsions and disturbances of consciousness related to the toxicity of hyperbaric oxygen - 2 persons (0.1%);
- dyspnoea resolving after leaving the chamber - 2 people (0.1%);
- chest pain with acute coronary syndrome - 1 person (0.05%).

During HBOT, 4 (0.2%) people were diagnosed with claustrophobia. It was not considered a complication of hyperbaric treatment, but it resulted in discontinuations of treatment. Two patients reported claustrophobia before starting treatment. They were qualified for treatment because claustrophobia is only a relative contraindication in hyperbaric oxygen therapy, especially in multi-site chambers. Both patients started treatment, however, even with sedatives, they were unable to attend the sessions [6].

The research conducted by Kobielska and Chrapusta shows that HBOT is a safe method with a low risk of complications, which can be used in many different acute and chronic diseases [6].

2.

Bessereau et. al. have conducted a 6-year prospective study on 150 patients (11 children and 139 adults) requiring mechanical ventilation during HBOT. The indications for the use of HBOT and the occurrence of side effects were analyzed. The results were compared according to the presence or absence of acute respiratory distress syndrome (ARDS). The main causes of intubation and mechanical ventilation were carbon monoxide poisoning (51%) and iatrogenic gas embolism (33%). ARDS occurred in 35 patients. ICU mortality in the ARDS group reached 23%. Side effects observed during the study were: cardiac arrest in 2 patients (1.6%); seizures in 2 patients (1.6%) and severe shock despite inotropic drugs in 3 patients (2.4%). Seizures only occurred in people with IGE [1].

3.

Ventilator-associated pneumonia (VAP) is the leading cause of serious infections in the ICU and is associated with significant morbidity. The use of HBOT in patients undergoing mechanical ventilation may increase the exposure to some risk factors, such as hyperoxemia and the need for multiple transfers. In their retrospective observatory research, led on 10-bed ICU, Caplan et al. evaluated the relation between HBOT and VAP. Patients who received mechanical ventilation (MV) for more than 48 hours were enrolled in the study. VAP was assessed based on clinical and radiological criteria. 42 (23%) of 182 patients enrolled in the study experienced at least one episode of VAP. HABOT was received by 124 (68%) patients. The frequency of VAP was 34 per 1000 days of ventilator use. The occurrence of VAP was significantly associated with immunosuppression, duration of MV, length of stay, re-intubation, in-hospital transport, use of paralysing drugs, tracheotomy, and prone position. The conducted research prompts the authors to question the influence of HBOT on the frequency of VAP in the analysed ward, where 2,500 HBOT sessions are performed each year in patients, half of whom are ventilated and intubated. The occurrence of VAP was not associated with the use of HBOT. More experimental and clinical research is needed to understand the effects of HBOT on the incidence of VAP and on the physiological microbiome [3].

Oxygen therapy is a common form of treatment in intensive care. It prevents hypoxia and improves the distribution of oxygen in the tissues. However, studies suggest an association between exposure to hyperoxemia and worsening prognosis in various situations. Even moderate hyperoxemia (arterial oxygen partial pressure (PaO_2)> 100 mmHg) is associated with increased mortality. In a meta-analysis cited by Caplan et al., involving more than 16,000 ICU patients, patients treated with oxygen had a dose-dependent increased risk of short- and long-term mortality. In critically ill patients, exposure to hypoxaemia may lead to various consequences, e.g., changes in mucociliary clearance and cellular immunity, reduction in surfactant synthesis, and denitrification promoting atelectasis. They can cause acute hyperoxic lung injury and contribute to the development of VAP [3].

The study by Hadanna et al. and Thorsen et al. presented by Caplan et al. showed that 60 daily sessions in 2 ATA with 100% oxygen had no significant effect on forced vital capacity and lung function. This supports the hypothesis that hyperoxemia, used in hyperbaric therapy, does not adversely affect the dynamic volume of the lungs [3].

4.

In case of carbon monoxide poisoning oxygen hyperbaric therapy is widely used in the prevention of delayed neuropsychiatric syndrome. Cho et al. in their work described the case of a 31-year-old man diagnosed with CO poisoning undergoing HBOT in a multi-site

chamber. The first HBOT session was uneventful. During the second HBOT session, the patient experienced sudden seizures. The doctor administered propofol to stop the convulsions and discontinued the HBOT. Soon after the seizures, the patient developed foamy discharge in the endotracheal tube and impaired oxygenation. No abnormalities were found in computed tomography of the head, which suggests a connection between the seizure and the use of HBOT. The chest X-ray revealed bilateral pulmonary oedema. Echocardiography showed no cardiac dysfunction, indicating that the pulmonary oedema was due to HBOT. The patient's respiratory condition improved. The seizure did not recur. No subsequent neurological sequelae were observed either. The presented unexpected adverse events, convulsions and pulmonary edema, are extremely rare during HBOT and their concomitant occurrence has not been reported. The major complications of HBOT include barotrauma and oxygen toxicity.

The exact mechanism underlying HBOT complications is not fully understood. In this case, convulsive seizures are believed to be related to CNS oxygen toxicity, as they did not occur prior to initiation of therapy and did not recur after stopping HBOT, and there was no other clear cause for their occurrence in the patient [9].

5.

HBOT is increasingly used in medicine to enhance the formation of collagen matrix and angiogenesis, which promotes the healing of wounds and necrotic tissues. Oxygen may also be associated with increased production of oxygen free radicals and oxidative stress. The imbalance in the production of free radicals causes a harmful modification of biological macromolecules. Studies from the last 50 years have shown the participation of free radical production in the emergence of an increasing number of diseases, such as hyperoxic lung disease, atherosclerosis, early retinopathy, Parkinson's disease and some forms of cancer. A reliable measure of the oxidative stress assessment are F2-isoprostanes (F2-IsoPs) formed as a result of non-enzymatic oxidation of arachidonic acid (AA). Under high oxygen pressure conditions, isofurans (IsoF) are formed from AA and better reflect the oxidative stress under high oxygen pressure conditions. A study by Corcoran et al. Measured IsoF and F2-IsoP in plasma in patients receiving HBOT for the treatment of osteonecrosis secondary to radiotherapy. Blood samples were taken from 12 patients (9 men and 3 women) before, during and after HBO treatment, which lasted 119 minutes. Seven serial blood samples were taken. The reason for using HBOT was radiation cystitis (6 people), tooth extraction (4 people) and osteoradionecrosis prophylaxis (2 people). The hypothesis was that as the oxygen pressure increases, the IsoFs will continue to increase, in contrast to the F2-IsoP, the synthesis of which will decrease. However, no significant changes in plasma IsoF or F2-IsoP were observed during the HABOT session. In this study, HBOT at a pressure of 2.4 atm and a maximum of 100% oxygen did not worsen the oxidative stress assessed by plasma F2-IsoF and IsoP. The lack of an increase in IsoFs or F2-IsoPs in the study suggests that although HBOT increases oxygen partial pressure with benefits for a wide variety of cellular processes, there is an antioxidant capacity to prevent increases in oxidative stress throughout the body.

The use of oxygen, especially under super-physiological pressure, may increase systemic oxidative stress and lead to overproduction of oxygen free radicals. She was informed prior to treatment that this was common and usually returns to normal after treatment. After several dozen HBOT treatments, the patient noticed dramatically decreased vision in both eyes. I was diagnosed with binocular advanced cataract accelerated by HBOT. The purchase of multi-focal glasses was recommended. The patient reported unsatisfactory vision even with glasses. Cataract extraction was performed by phacoemulsification and an intraocular lens was placed in one eye and surgery on the other eye was scheduled later. The leg ulcer healed completely. The literature reviewed by the authors shows that this is the earliest case of cataract formation. It has been hypothesized that in the case of cataracts during HBOT, the generated oxygen free radicals can damage many tissues, especially the delicate lens. During HBO2 therapy, most often after long-term procedures, cataracts may develop or be accelerated. In the study by Palmquist et al. cited by Hagan et al. conducted on 15 patients who underwent ophthalmological examinations before HBOT, without diagnosed cataracts, in 7 (46.6%) after 150 procedures, the development of not fully reversible cataracts was found. The incidence of cataracts during and after HBOT is not fully understood, but it may be permanent and progressive. Before using HBOT, a complete, extended ophthalmological examination should be considered [14].

8.

The aim of the paper by Jakinena et al. was to analyse the frequency of adverse events during hyperbaric oxygen therapy in 2012-2015. In this analysis, events were defined as ear / sinus barotrauma, ventricular confinement anxiety, hypoglycemia, oxygen toxicity, pneumothorax, seizures, and dyspnoea. A retrospective study was conducted. The data for analysis was taken from health records containing information on 1,529,859 hyperbaric treatments used during 53,371 treatment courses in outpatient wound care centres in the United States. Of 1.5 million HBOT procedures, 0.68% were associated with adverse events. The most commonly reported events were barotrauma and confinement anxiety. Serious adverse events were extremely rare, with less than 0.05 cases of oxygen toxicity per 1,000 procedures and only 1 confirmed case of pneumothorax. In this study, barotrauma was defined as a complication of pressure equalization in the middle of the ear or sinus. Patients typically reported pain related to inability to equalize pressure in the ears. Fear of incarceration was identified when a patient in the chamber verbalized or signaled a desire to end treatment due to claustrophobia. Hypoglycaemia without accompanying seizures has been identified with blood glucose levels less than 70 mg / dL in diabetic patients.

Oxygen toxicity was identified by: blurred or tunnel vision, irritability (i.e. a marked change in behaviour), nausea, facial tremors, ringing or tinnitus, and dizziness. Adverse events were extremely rare during HBO therapy. During 99.3% of all HBOT procedures, no adverse event was recorded. The most frequent events were ear / sinus barotrauma (0.37%), followed by anxiety related to occlusion (0.16%) and symptomatic hypoglycaemia (0.08%). More serious events such as seizures (0.02%) and non-seizure oxygen toxicity (0.01%) were very rare. Pulmonary barotrauma was

identified only in 1 case. Treatment related to the adverse event was shorter than without. Treatments where the patient complained of barotrauma and the fear of confinement had the shortest average duration, just over an hour. Patients were less prone to adverse events during treatment. HBOT treatments in which an event occurred were more frequently observed at higher pressure values, confirming previous findings that the risk of an event increases with increasing pressure. Patients experiencing the events typically had slightly more than 1 event per treatment cycle. The results of the conducted study indicate that the occurrence of HBOT-related adverse events is rare and usually harmless. The use of HBO therapy in accordance with appropriate therapeutic protocols is a safe procedure with a low risk of complications. Patient education and pre-treatment precautions will help with some of the more common events, such as shutdown anxiety and hypoglycaemia, which may be further reduced [7].

9.

Lin et al. conducted przeprowadzili a systematic review of the literature and a meta-analysis of randomized controlled trials assessing HBO therapy and its impact on neuropsychometric dysfunction following CO poisoning. A comparison was made of neuropsychological dysfunctions in 492 patients (from two studies) with more severe CO poisoning, who initially lost consciousness or were in a coma and received 1 or 2 HBOT sessions. Both studies showed that 2 HBOT sessions had no advantage over 1 session. Memory impairment (8.9% vs 18.3%) and difficulty concentrating (6.1% vs 13.4%) were significantly lower in the group that received one session of HBO treatment compared to the group that received two sessions [8].

10.

In their work Meng et al. investigated on 90 patients (53 patients who were administered plums and 37 patients in the control group) the effect of consumption of dried salted plums on MEB and otalgia associated with HBO2 therapy. The overall prevalence of MEB after the first HBOT session was 38.9%.MEB occurred in 39.6% of patients treated with plum and in 37.8% of patients in the control group. Otalgia occurred in 5.7% of patients treated with plum and in 18.9% of patients in the control group. The severity of otalgia was higher in the control group. The conducted research shows that consumption of dried salted plum does not reduce the incidence of MEB, but may alleviate its severity. The authors found that the incidence of otalgia after the first HBO session was 11.1% lower than the incidence of MEB. The prevalence of MEB in previous studies ranged from 8% to 68.7% [11].

11.

People under HBO2 therapy cannot develop decompression sickness (DCS) because oxygen is consumed in the tissues and there is no possibility of supersaturation. Arterial gas embolism (AGE) is possible during HBO2 therapy due to pulmonary barotrauma (damage due to stretching of the lungs during decompression in HBOT). Moon in his work emphasized that during his over 30 years of care for patients undergoing HBOT and volunteers tested in hyperbaric chambers, there were only two cases of gas embolism due to exposure in a hyperbaric chamber (compared to several thousand due to diving and / or accidental intravascular air injection). Both cases occurred due to a rupture of pulmonary cysts in patients with severe lung disease who were at particular risk of developing these types of complications. About 1.3 million hyperbaric treatments are performed annually in the USA. The risk of AGE from HBOT is likely to be less than one in several million treatments. Paralysis due to gas embolism from HBOT is extremely rare and its risk can be controlled by patient selection [15].

12.

Middle ear barotrauma is a common complication of ventricular compression in hyperbaric oxygen therapy. There is little evidence on the optimal compression protocol to minimize the incidence and severity of MEB. Ng et al. compared the frequency of MEB occurrence during hyperbaric oxygen therapy using two different ventricular compression protocols in a single-center, double-blind, randomized controlled trial on 100 participants (74 men and 26 women) undergoing the first HBOT session. Patients were randomly assigned to a graded (n = 50) or linear (n = 50) compression protocol. Photographs of the eardrums were taken before and after treatment and then scored. The incidence of MEB in the staged protocol was 48% (in 24 subjects), and in the linear protocol was 62% (in 31 subjects). Thus, the staging protocol did not show a significant reduction in the occurrence of MEB compared to the gold standard, the linear protocol. The staged protocol, however, reduced the severity of symptoms in MEB compared to the linear protocol. Eight subjects (16.0%) in the staged compression group and 12 subjects (24.0%) in the linear compression group did not continue the treatment. 1 participant (2.0%) in the staged group and 3 participants (6.0%) in the linear group did not complete the treatment. Painless hyperbaric treatment was reported in 84% (42 people) according to the staged protocol and 88% (44 people) according to the linear protocol. In order to minimize middle ear barotrauma, further research is needed to determine the optimal compression protocol [16].

13.

Tran and Smart described in their study the case of a 43-year-old man with type 2 diabetes, treated with insulin for 28 years, who suffered from treatment-resistant bilateral plantar ulcers. The patient was scheduled for 40 sessions of hyperbaric oxygen treatment at a pressure of 243 kPa for 90 minutes. The patient's ophthalmic history revealed the presence of bilateral proliferative diabetic retinopathy (PDR) three years earlier, which was treated by panretinal photocoagulation (PRP). Three months before HBOT was used, the patient underwent phacoemulsification and the insertion of an intraocular lens in the left eye. The same procedures had been done a year before in the right eye. One week before his first HBOT session, the patient underwent a fundus examination which confirmed non-proliferative diabetic retinopathy (NPDR) without PDR symptoms. After the fifth HBOT session, the patient underwent a routine ophthalmological check-up. A fundus examination revealed pre-retinal haemorrhage and PDR in the left eye. Treatment with PRP was applied. Visual acuity has not changed. During the examination three weeks later, after another 12 HBOT sessions, increasing proliferative changes in both eyes were found. Bevacizumab was injected and PRP was applied. Visual acuity in both eyes remained unchanged. HBOT was withheld to resolve the

proliferative phase of retinopathy. It is unclear whether the sudden progression of NPDR to PDR was associated with HBOT, recent cataract surgery, or other factors [17].

14.

Uluyol et al. performed a study of 47 non-diabetic patients treated with HBO to evaluate the effect on the nasal mucociliary clearance (MCC) of short- and long-term exposure to hyperbaric oxygen. The participants, according to the adopted number of HBOT sessions, were divided into 2 groups. The short-term HBOT group consisted of 19 patients who received <11 HBOT sessions. The long-term HBOT group consisted of 28 patients who received more than 15 sessions. The mucociliary clearance was measured in patients 3 times: before, after completion and 6 months after HBOT. Both short- and long-term exposure to HBO had an important impact on MCC after ending the treatment. Only long-term exposure to HBO prolonged the MCC in the long-term assessment (6 months after HBOT). Based on the results, the authors concluded that long-term exposure to HBO can cause irreversible damage to the MCC compared to short-term exposure, and that HBOT affects MCC in a dose-dependent manner. This is alarming because of the prevalence of middle ear, paranasal sinus or respiratory infections in patients undergoing HBOT. With long-term use of HBOT, patients should be monitored and informed about the possible negative effects of the therapy. MCC is an essential defense mechanism in the respiratory system. Abnormalities in MCC lead to residual secretions and recurrent infections of the middle ear, sinus and lower respiratory tract. Impairment of MCC may result from impaired ciliary movement or increased mucus viscosity. Patients undergoing HBOT should be monitored and informed about possible side effects [18].

15.

Wang et al. Assessed the effect of HBOT on the progression of latent tuberculosis infection (LTBI) to active tuberculosis (TB). The authors analysed 2,258 patients divided into two groups: the group of patients undergoing HBOT and the group of patients without HBOT.Each group consisted of 1129 patients. One year after the use of hyperbaric oxygen, the number of cases of active tuberculosis was significantly higher in the HBOT group compared to the group without HBOT (11 cases vs. 1 case). Multiple regression analysis showed that hyperbaric oxygen therapy was the only statistically significant factor influencing tuberculosis activation. The conducted research shows that HBOT will reactivate tuberculosis. Patients at high risk of tuberculosis should undergo a tuberculin test or interferon-gamma release testing prior to HBOT to identify individuals with LTBI [19].

16.

Seizures associated with oxygen poisoning are a known complication of hyperbaric oxygen therapy. Warchol et al. reported a case in which a seizure and a stroke occurred together. The authors believe that the stroke may have been caused by seizure-induced ischaemia. This challenges the accepted view that seizures in oxygen poisoning during HBOT are mild. An 80-year-old man after a cerebrovascular accident (CVA) without residual deficit, with mild chronic obstructive pulmonary disease (COPD), coronary artery disease, chronic kidney disease and peripheral vascular disease, underwent hyperbaric oxygen treatment for a non-healing toe ulcer with due to arterial insufficiency. The patient underwent the first HBOT session (90 minutes at 243 kPa) in a single-site chamber without any incidents. The patient tolerated the second procedure well until decompression. At the end of decompression, staff noticed that the patient was unresponsive, with aphasia, inability to obey commands in the left upper limb, spastic, clumsy right hand movements, and rhythmic smacking movements. The patient developed a tonic-clonic seizure lasting approximately 90 seconds. The patient was thought to have developed a seizure during HBOT as a result of CNS oxygen toxicity. The seizure was believed to have influenced the onset of a stroke. Further HBOT sessions were judged to be of greater risk than benefit, and treatment was discontinued. There have been no previous reports of an acute cerebral ischaemic event as a result of an epileptic seizure in oxygen poisoning associated with HBOT. Seizures during HBOT are a known complication and occur at a frequency of 0.03%. The incidence increases with pressure and may be almost absent at or below 202 kPa (2.0 ATA). Reducing the therapeutic pressure can greatly reduce or eliminate the risk of a seizure. Epileptic seizures of oxygen poisoning are most often manifested by tonic-clonic seizures, but focal seizures can also occur. In the analyzed case, the patient had both lip twitching and a tonic-clonic seizure [20].

17.

Metronidazole (MNZ) is prescribed for the treatment of infections caused by anaerobic bacteria and protozoa. Metronidazole-induced encephalopathy (MIE) is a side effect of this medication. In their work Yamamoto et al. presented the case of a 68-year-old man with osteomyelitis, who received metronidazole and the HBO therapy (2.0 ATA, 60 min) five times for 49 days. 47 days after starting treatment with metronidazole. After treatment with HBO five times, the patient developed MIE symptoms (peripheral neuropathy, speech disorders, nausea, hearing loss and gait disturbance). After stopping both MNZ and HBOT therapy, neurological symptoms quickly improved within 5 days. Peripheral neuropathy lasted for several weeks. This is the first reported case of MIE associated with HBOT. Although HBO therapy is effective in treating osteomyelitis, it may be one of the risk factors for MIE [20].

18.

In a prospective study by Lee et al. On 1,308 patients (10,425 treatments) who received HBOT, 5 had seizures (patients with CO poisoning: n = 4; patients with arterial gas embolism: n = 1). Seizure frequency in patients with CO poisoning (0.148%) and AGE (3.448%). None of the patients had lasting effects due to the seizures. Seizures have been observed in patients with CO and AGE poisoning [21].

19.

Edinguele et al. conducted a five-year retrospective study on 2610 patients. 262 patients (10.04%) experienced MEB while on HBOT. Women were more affected by this complication than men. The risk factors were: age over 55, female gender, diseases of the ear, nose and throat (cancer, infections or allergies, malformations or benign neoplasms) and diseases of other systems and addictions (smoking, obstructive

breathing disorders, thyroid disorders, obesity). During HBOT sudden deafness, altered mobility of the eardrum and delayed wound healing occurred. The MEB event was responsible for premature discontinuation of HBOT [22].

20.

Churchill et al. analysed adverse events (AEs) in two randomized, double-blind clinical trials conducted with HBOT. In both studies, participants were randomly assigned to receive HBO2 (1.5 atmospheres absolute,> 99% oxygen) or sham chamber sessions (1.2 absolute atmospheres, room air). In 143 subjects who underwent 4,245 sessions in a hyperbaric chamber, ventricular adverse events were rare (1.1% in the first study, 2.2% in the second study). The most often problem reported was mild barotrauma. Some participants experienced a headache from time to time during the sessions. There were no serious adverse events associated with chamber sessions [23].

21.

Nasole et al. conducted a retrospective observational study in 5962 patients undergoing long-term HBO2 therapy for chronic diseases to analyze the frequency and severity of MEB. Over the course of eight years, he observed 549 MEB (9.2% of all HBOT treatments). Most of them were female patients over 50 years of age. Symptoms of MEB were most often mildly severe with minimal otoscopic changes. 69.03% of cases were classified as Wallace-Teed grade 1. MEB was recorded in 20.3% of patients who had difficulty equalizing the pressure in the ears and / or experienced ear pain in the initial phase of compression during hyperbaric treatment. Inflammatory diseases of the upper respiratory tract, especially rhinitis, predispose to the development of MEB. MEB led to the suspension of therapy in 89 patients, which accounted for 16.2% of all registered MEB or 1.49% of all patients undergoing HBOT procedures [24].

22.

In their research Fan et al. described the case of a 56-year-old patient who suffered severe pulmonary oedema after HBO2 therapy due to carbon monoxide (CO) poisoning. After HBOT (100% oxygen at 0.25 MPa, 60 minutes with a five-minute air break and decompression at 0.01 MPa / minute), the patient suddenly developed dyspnoea. After the therapy, the heart rate was 140 beats per minute, blood pressure - 60/40 mmHg, respiratory rate - 38 per minute and oxygen saturation - 84%. Acute pulmonary oedema and shock were diagnosed. Anti-shock treatment, endotracheal intubation, mechanical ventilation to support respiration, diuretics, dexamethasone, asthma relief and acidosis correction were applied. CT scan showed significant pulmonary oedema. The patient gradually recovered. During the two-year follow-up, the patient did not report any psychological or neurological symptoms. Acute pulmonary oedema during HBOT is rare but can lead to serious side effects in patients with severe acute CO poisoning. This complication should be considered when administering HBOT to patients with severe CO poisoning [25].

23.

In their research Gariel et al. presented the case of a 57-year-old woman who was admitted to the intensive care unit in a state of severe hypotensive shock after an HBOT session. The shock was attributed to gastric barotrauma, which resulted in massive venous gas embolism. Gastric barotrauma occurred due to the presence of a filled gastric band / cuff during HBOT, which prevented expansion gas from escaping during decompression. After deflation of the gastric banding, two additional HBOT sessions were performed. Symptoms completely resolved. On the third day, the patient was discharged from the hospital without symptoms. Due to the risk of gastric barotrauma and venous gas embolism, physicians should be aware of the history of the gastric banding before starting HBO therapy[26].

24.

The increase in blood pressure in patients undergoing HBO therapy is a less defined potential side effect. Heyboer et al. tried to better quantify the effect of HBO2 on blood pressure in patients undergoing HBOT. They conducted a retrospective study on 155 patients who received 3,147 hyperbaric oxygen treatments. They observed an overall increase in systolic blood pressure, diastolic blood pressure and mean blood pressure after treatment. There was no statistically significant difference between patients with and without hypertension. The change in SBP was less with each subsequent treatment in patients receiving more than one treatment. The study shows that an absolute increase in blood pressure can occur as a result of HBO therapy. However, the scale of this effect is not large. A protective effect appeared with more treatments [27].

25.

When side effects occur during HBOT treatment, the therapy should usually be discontinued or delayed. Delays in HBOT due to Eustachian tube dysfunction (EDT) occur in about 10-40% of patients. Cohn et al. Carried out a retrospective analysis of 81 patient cards in terms of risk factors and symptoms of HBOT- related side effects, such as EDT and middle ear barotrauma. A total of 31 (38.3%) did not tolerate HBOT. In 8 of them, the situation improved after the use of oxymetazoline, and in 23 of them a tympanostomy tube was inserted. The susceptibility to complications in patients intolerant to HBOT was higher compared to patients who tolerated the therapy. Patients with a history of otitis media, tinnitus, and previous ear surgery were at risk of HBOT intolerance. Accurate otological evaluation may influence the prediction and identification of patients at risk of HBOT intolerance. The use of a tympanostomy tube should be taken into account in people intolerant to HBOT, who require long-term therapy, already at the first or second session [28].

26.

The study by Lu et al. presents the case of a 72-year-old woman treated with sudden hyperbaric oxygen recompression (HBO2 RCT) after the occurrence of paralysis of the lower limbs, after exposure to hyperbaric air in a home hyperbaric chamber. After undisturbed exposure to hyperbaric air at a maximum depth of 72 feet (3.2 ATA, 32.3 psig), the patient had delayed abdominal pain and post-meal paraplegia. After HBO2 RCT, the patient recovered completely. The presented case corresponded to the term - "disturbed decompression". With limited blood volume and the need for simultaneous perfusion of two "intermediate" tissues, according to the authors, a "theft" syndrome arises, causing abdominal symptoms and paralysis [29].

27.

Hyperbaric assistants work in a hyperbaric environment to provide medical care to patients during treatment in a hyperbaric chamber. While patients breathe 100% oxygen during HABOT, assistants breathe compressed air for almost the entire session while remaining at the same pressure as patients, an experience similar to that of divers breathing with a compressed air cylinder. The retrospective study by Poolpol et al. was aimed at examining the long-term changes in lung function in people working in hyperbaric conditions. 63 people working in multi-seat hyperbaric chambers who worked in public hospitals or medical centres in Thailand were included. 51 people met the criteria for inclusion in the study. To participate in the study, subjects were required to have at least two follow-up pulmonary function tests and a minimum gap of one year from the initial annual periodic test. Lung function of hyperbaric chamber workers was compared with the reference values of the Thai population. The authors showed that working in a hyperbaric environment affects the lung function of assistants in hyperbaric chambers during HBOT. Pulmonary function changes depended on total working time, mean session duration, and mean depth of hyperbaric therapy. In addition to assessing the working capacity of assistants, periodic lung function assessments should be encouraged to monitor for further possible harm [30].

SUMMARY

HBOT is one of the safest therapies in use today. The described side effects are often self-limiting and can be avoided by appropriate screening tests. Side effects of HBOT include various forms of barotrauma, CNS and pulmonary oxygen toxicity, ocular disorders, and claustrophobia. The most common are middle ear barotrauma and claustrophobia. Pulmonary barotrauma is unlikely with proper precautions. Middle ear barotrauma is usually mild and self-limiting. It can be prevented by teaching middle ear cleaning techniques, regulating ear pressure, and assisting with compression. Claustrophobia can be regulated with coaching and anti-anxiety medications. In the case of intolerance to a one-place chamber, the patient may be referred to the nearest multi-place chamber. Oxygen toxicity is rare and most often affects the central nervous system. Symptoms resolve with oxygen withdrawal and leave no lasting consequences. Pulmonary barotrauma is an unlikely complication and can be avoided with appropriate screening tests. Hyperoxic myopia is also one of the most common side effects considered to be reversible. Clinically significant hypoglycaemia is not common [10]. Hyperbaric oxygen therapy is currently approved for the treatment of a variety of conditions and is widely used to treat selected chronic wounds, delayed radiation injuries, and necrotic soft tissue infections [7].

Studies show that the incidence of HBOT-related adverse events is low and usually mild [7].

CONCLUSIONS

- HBOT is a safe and well-tolerated method of treatment of various diseases.
- Adverse events connected with HBOT are rare and are usually mild.
- The most common side effects associated with HBOT are middle ear barotrauma and claustrophobia.

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