



## HYPERBARIC OXYGEN THERAPY – PART 2. POSSIBILITIES OF USE IN MEDICINE

Hiperbaryczna terapia tlenowa – cz. 2.  
Możliwości wykorzystania w medycynie



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### Abstract

The growing interest in the use of hyperbaric oxygen therapy in medicine prompted us to analyse the available research reviews and meta-analyses and to systematize data on hyperbaric oxygen therapy. The second part of the article presents the use of hyperbaric oxygen therapy in the treatment of burns and skin grafts, difficult-to-heal wounds, diabetic foot ulcers, air embolism, decompression sickness, anaemia, genitourinary disorders, carbon monoxide poisoning, chronic osteomyelitis, gas gangrene, radiation necrosis and anal fistulas.

### Streszczenie

Wzrost zainteresowania wykorzystaniem hiperbarycznej terapii tlenowej w medycynie skłonił autorów do przeanalizowania dostępnych przeglądów badań i metaanaliz oraz uszeregowania danych na jej temat. W drugiej części artykułu przedstawiono zastosowanie hiperbarycznej terapii tlenowej w leczeniu oparzeń, przeszczepów skóry i trudno gojących się ran, zespołu stopy cukrzycowej, zatorów gazowych, choroby dekompresyjnej, niedokrwistości, chorób układu moczowo-płciowego, zatruc czadem, przewlekłych zapaleń kości i szpiku, zgorzeli gazowej, martwicy popromiennej oraz przetok odbytu.

**Keywords:** wound healing, hyperbaric oxygen therapy, osteomyelitis, osteoradionecrosis, gas gangrene, radiation necrosis

**Słowa kluczowe:** gojenie ran, tlenowa terapia hiperbaryczna, zapalenie kości i szpiku, martwica popromienna kości, zgorzel gazowa, martwica popromienna

DOI 10.53301/lw/171424

Received: 06.07.2023

Accepted: 21.08.2023

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### Introduction

The first part of the paper was a historical overview of research on hyperbaric oxygen therapy (HBOT), the mechanism of a hyperbaric chamber, as well as indications and contraindications for this form of treatment. Part two discusses the use of HBOT in various medical fields except for the treatment of diving incidents (including decompression sickness and arterial gas embolism) as this is well known.

### HBOT for burn treatment

A burn is an injury to the skin or, depending on the severity, deeper tissues, characterised by the presence of a necrotic zone surrounded by the zones of stasis and hy-

peremia (hypoperfusion) accompanied by oedema [1]. A correlation between increased hypoxia and impaired wound healing has been demonstrated [2]. HBOT is used in the treatment of burns of various aetiologies to reduce oedema, improve blood flow and reduce fluid loss due to vascular damage [3]. In order to achieve an optimal effect, HBOT should be included in surgical and symptomatic treatment as soon as possible, preferably within 24 hours. HBOT is also used for bronchial burns, where, in addition to reducing oedema, preventing anaerobic bacterial growth is an equally important factor [4].

Knefel et al. assessed comprehensive treatment in a group of patients with electrical burns, where 21 out of 61 patients additionally received HBOT, showing that the latter method improved overall treatment efficacy.

There were no cases of mortality in the HBOT group and the rate of late infectious complications was almost twice as low. However, there were some negative effects compared to the control group in terms of a higher number of necessary amputations and longer hospital stays, which were however blamed on the worse baseline clinical condition of these patients [3]. HBOT is also used in the treatment of pain in third-degree burns. A rat study published in 2019 suggested that prolonged use of this method may reduce burn-induced mechanical allodynia [5]. Early HBOT often allows for avoiding intubation in patients with airway burns. Furthermore, it can be used in already intubated patients [6].

However, since not all studies to date have been of good methodological quality and have sometimes yielded contradictory results, research on the efficacy of HBOT in burn care should continue [7].

### HBOT for skin grafts

Although burns are a common indication for skin grafts, the latter represent a separate medical problem. HBOT can be used during allogeneic skin grafting. Misiuga et al. assessed HBOT-assisted burn therapy in terms of the time of graft adherence to the wound bed, length of hospital stay and the number of autologous skin graft procedures in two 20-patient groups. The study showed statistically significant differences in all three areas; HBOT-assisted treatment was associated with faster wound healing, shorter hospital stay and fewer autologous skin graft procedures compared to the standard treatment group [8].

The transplanted tissues vary in size, have an abnormal blood supply and the nutrient supply depends on the recipient's body. HBOT improves fibroblast function and thus increases neovascularisation and oxygenation of blood vessels and tissues [4]. HBOT offers the possibility of salvaging compromised grafts if the degenerated state of the recipient's wound bed was correctly and quickly diagnosed [2]. A study in rats showed that HBOT promoted neovascularisation of transplanted skin flaps, with laser Doppler imaging (LDI) showing an increase in tissue blood flow, consistent with histological findings [9]. The same study pointed to increased SDF-1 and CXCR4 protein expression as the cause of neovascularisation. Further studies on the use of HBOT in skin graft healing have shown a synergistic effect with subcutaneous hirudin [10]. HBOT allows stimulation of leukocyte function, suppression of exotoxin production and a synergistic effect of antibiotic therapy, demonstrating bactericidal activity against anaerobic bacteria. In clinical practice, HBOT has been used during surgical treatment in combination with negative pressure therapy, showing efficacy despite *Pseudomonas aeruginosa* infection [11].

### HBOT for difficult-to-heal wounds

Difficult-to-heal wounds are another challenge of modern medicine. Advanced age, overweight and obesity (poorer blood supply to adipose tissue), chronic comorbidities (e.g. diabetes), poor nutritional and hydration status, smoking and coinfections are factors that correlate with an increased risk of difficult wound healing [12].

Wound oxygenation status is a determinant of healing outcomes, with wound hypoxia correlated with impaired healing. Oxygen supply, on the other hand, accelerates the wound healing process [4]. Furthermore, the use of HBOT in the treatment of difficult-to-heal wounds increases nitric oxide (NO) production, which contributes to the efficiency of the healing process [13]. In their meta-analysis, Longobardi et al. demonstrated the efficacy of HBOT in the treatment of delayed healing ulcers [14]. As pointed out by the authors, the HBOT protocol should be based on the outcomes of standard comprehensive treatment. HBOT should be considered when there is no response to standard therapy after 4–6 weeks [14, 15].

Single clinical case reports confirming the efficacy of HBOT (usually  $\geq 30$  sessions) in the treatment of chronic wounds in children may also be found [16].

### HBOT for diabetic foot ulcers

HBOT is used to improve the healing process of ulcerative wounds and necrotic soft tissue lesions within the foot that develop as vascular complications of diabetes (diabetic foot ulcers, DFUs) [4]. Knefel et al. included 24 patients (11 women and 13 men; mean age 48 years) in their study. DFUs were managed with pharmacotherapy, surgery and HBOT. Local lesions resolved completely and radically in 5 and 8 patients, respectively, while elective amputation was prevented in 5 patients [17]. Kaplan et al. used HBOT as adjunctive treatment in 146 diabetic foot patients. Full recovery and significant improvement were reported in 69.6% and 17.9% of patients, respectively [18].

In their meta-analysis of 20 randomised clinical trials, Zhang et al. showed statistically significant differences in HBOT-assisted therapy for DFUs compared to standard treatment alone. These studies have shown the benefits of HBOT in terms of faster wound healing, a reduced risk of major amputations and pain relief [19].

The use of HBOT as an adjunctive treatment for DFUs appears to be a common and proven standard. However, there are some discrepancies in the literature regarding the improvement of quality of life [20] and reducing the number of total amputations [21].

### HBOT for anaemia

HBOT can be used in anaemic patients with increasing oxygen debt (symptoms such as tachycardia, dyspnoea, fatigue, chest pain, metabolic acidosis and increased cardiac enzymes) who cannot receive packed red blood cells (PRBCs) (due to religious beliefs or massive autoimmune haemolysis [22]), as well as in patients on the waiting list for compatible blood products [23]. Importantly, pulse-flow (intermittent) oxygen supply (normo- or hyperbaric) induces an increase in RBC count in patients with both acute and chronic anaemia [24].

### HBOT for genitourinary disorders

There are also many reports on the use of HBOT in genitourinary disorders, including:

- Fournier's gangrene [25], where HBOT reduces both length of hospital stay and the extent of limb amputation [4];
- cystitis (radiation-induced, interstitial and haemorrhagic [26]), where HBOT limits tissue inflammation, oedema and capillary pressure, as well as promotes activation of fibroblasts and reversal of negative changes associated with abnormal angiogenesis [26];
- pelvic radiation disease following radiation therapy (radiation proctopathy);
- dystrophic calcifications of the prostate.

Further indications include priapism (a case report of an 11-year-old boy with sickle cell anaemia [27]) and erectile dysfunctions (secondary to urethral repair) [26]. HBOT has also been suggested for overactive bladder syndrome and chronic pelvic pain [25].

### HBOT for CO poisoning

HBOT is a well-established treatment for carbon monoxide (CO) poisoning, significantly reducing mortality [4]. Short-term exposure to CO causes influenza-like symptoms, headaches and cognitive impairment, whereas long-term exposure is associated with neuro- and cardiotoxic effects [28]. Unfortunately, up to 30% of recovered patients [28] experience neurocognitive complications (headaches, irritability, personality disorders, confusion, memory loss [29], sleep disorders and impaired concentration, psychotic symptoms and parkinsonism [28]) for up to a year after CO poisoning, which may develop immediately after poisoning or within days to weeks afterwards [28, 29]. The prevention and treatment of these complications is a major area of research on the use of HBOT in this group of patients [29].

### HBOT for osteomyelitis

HBOT is successfully used as an adjunctive treatment (in parallel to antibiotic therapy and surgical wound debridement) in patients with chronic refractory osteomyelitis (which is most commonly caused by *Staphylococcus aureus* [30], but there are also case reports on *Streptococcus pneumoniae* aetiology [31]), as a complication of open bone fractures or intraoperative infection. The use of HBOT was assessed in patients with grade III and IV osteomyelitis (Cierny-Mader classification system) of the femur [32], tibia [33] and ankle [31]. The beneficial effects of HBOT in osteomyelitis are attributed to the activation of neutrophils, inhibition of bacterial pathogens, enhancement of antimicrobial action and healing mechanisms, as well as reduction of inflammation. Adjunctive HBOT inhibited the infection in 60–85% of patients with chronic refractory osteomyelitis [34]. This is important as antimicrobials induce selection pressure among pathogenic microorganisms, resulting in the emergence of resistant strains (which is observed for all classes of antibiotics, regardless of chemical properties or molecular mechanisms [35]). Therefore, the incorporation of HBOT as an effective adjunctive treatment may enable a quantitative and qualitative reduction in the use of antimicrobials, which would certainly be in line with the mission of the National Program to Protect Antibiotics.

### HBOT in necrotizing soft tissue infections (gas gangrene)

HBOT is also used to treat necrotizing soft tissue infections (NSTI) involving the fascia, muscles, tendons, ligaments, etc. [31]. Early diagnosis and treatment are crucial, as shown in a Finnish study, where 12 (22.6%) out of 53 NSTI patients infected with *Clostridium perfringens* [36], responsible for 80% of cases [37, 38] (other culprits included *C. novyi*, *C. septicum*, *C. hemolyticum*, *C. sordelli* [38]), died after surgical debridement of the wound, broad-spectrum antibiotic therapy and HBOT (2.5 atm) [36]. The mortality rate is 100% in untreated patients, 25–30% with properly implemented treatment (a decrease to 20% has been reported in recent years [37]), and up to 5–10% with HBOT [38] (depending on the patient's general health condition, age, immune status and comorbidities [37]). Unfortunately, comprehensive treatment of NSTI with HBOT is usually not possible due to lack of reimbursement from social insurance (the costs of HBO treatment for NSTI patients is approximately 8,000–25,000 euros/patient [39]) and the method is not available in emergency/surgical departments. At the same time, any delay in surgical treatment due to the use of HBOT would be unacceptable [39], especially since, due to the rapid progression of NSTI, wound revision and repeated debridement is usually necessary after 4–6 hours [38].

### HBOT for radiation-induced necrosis of bone or soft tissue

Osteoradionecrosis (ORN) is among the most serious complications of cancer treatment, head and neck tumours in particular [40]. About 9% of patients in this group who received a radiation dose of >60 Gy will develop ORN [41]. Radiation therapy results in vascular endothelial inflammation and obliteration, as well as tissue hypoxia, which leads to fibroblast dysfunction and subperiosteal fibrosis, death of osteoblasts and osteoclasts, and bone marrow atrophy, in line with the "3H rule: hypovascular, hypocellular, hypoxic" [40]. If no spontaneous healing occurs, chronic osteomyelitis develops, which can lead to mandibular fracture and soft tissue necrosis [41]. It should be noted that patients are usually unaware of ORN, with a non-healing wound after tooth extraction being the first sign of the disorder [40]; therefore, it seems important to assess the impact of prophylactic HBOT. Shaw et al. [42] conducted their study in 100 patients following radiotherapy to the head and neck (>50 Gy), who required tooth extraction or implant placement in the mandible and were randomised into two equal groups. All patients received chlorhexidine (mouthwash) and antibiotics. The study group additionally received HBOT (2.4 atm, 80–90 minutes for 30 days). Six months postoperatively, there was a similar number of patients with ORN in the study group (6.4%) vs. control group (5.7%) based on blinded evaluation of clinical and radiographic images, quality of life, acute symptoms and pain intensity. It was found that HBOT could not replace surgery (removal of necrotic tissue [43]) and targeted antibiotic therapy [41, 43] in ORN, and its efficacy was comparable to that of pharmacotherapy (antibiotics and antifibrotics) [43].

**HBOT for anal fistula**

HBOT is also used to treat anal fistulas [44] in the course of Crohn's disease, including those refractory to other forms of therapy. Since about 20–30% of patients in this group develop fistula at least once within 20 years of diagnosis [43, 45], it represents a serious medical and social problem. Although some cases are almost asymptomatic, a fistula can lead to pelvic abscess formation and sepsis [44]. Permanent remission is rarely achieved, with high recurrence rates necessitating re-intervention or stoma formation [45]. Lansdorp et al. [44] described a long-term (12 months) follow-up of 20 patients with at least one active, chronic (average of 4 years) treatment-resistant perianal fistula who received HBOT (2.5 atm, 80 min, 40 treatments over 8 weeks) as an adjunct to biological therapy. At week 16, significant improvement was observed in 13 of the 20 patients, expressed as a reduction in perianal disease activity index (7.5 vs. 4; a score  $\leq 4$  indicates remission), modified van Assche index (9.2 vs. 7.3), fistula drainage, as well as C-reactive protein (4.2 vs. 2.2 mg/mL) and faecal calprotectin (399 vs. 31  $\mu\text{g/g}$ ).

**Conclusions**

The current state of knowledge has prompted many researchers to seek HBOT-assisted treatments for various disorders. Such practice seems reasonable for difficult-to-heal wounds and skin grafts. There is, however, less evidence for the efficacy of HBOT in the treatment of anal fistulas and diabetic foot ulcers (there are discrepancies in the literature regarding improved QoL and number of amputations). It should be noted that although HBOT cannot replace routine treatment (e.g., in the case of ORN surgery), it may be used in parallel with standard of care in many cases. The rapid growth of interest in HBOT, evident in scientific publications in recent years, is a good prognosticator for the development of the method itself. However, although many studies on its utility (e.g., treatment of burns) still need to be continued, the procedure itself, due to its simplicity, versatility and accessibility, is likely to enjoy growing popularity in the coming years.

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