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Update on hyperbaric oxygen therapy in burn treatment

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Summary Hyperbaric oxygen therapy (HBOT) has been shown to improve tissue hypoxia, neovascularization and ischemia reperfusion injury and reduce pathologic inflammation in various clinical settings and was proposed to be a game changer in treatment of burns. Improved and faster wound healing as well as a reduction of morbidity and mortality after thermal and concomitant carbon monoxide poisoning are expected. In defiance of the observed benefits for burn wounds and carbon monoxide poisoning in animal models and few randomized controlled trials there is an ongoing controversy regarding its use, indications and cost effectiveness. Furthermore, the use of HBOT, its indications and the evidence behind its efficiency are still widely unknown to most physicians involved in the treatment of burn patients. Therefore, a review of the up to date evidence-based literature was performed with a focus on available data of HBOT in burn care, to elaborate its use in acute thermal injury and carbon monoxide intoxication. Although beneficial effects of HBOT seem very likely insufficient evidence to support or disprove the routine use of HBOT in the treatment of burn care was found. Although difficult to carry out because of the high interindividual variability of burns and chronic wounds, the need for larger high-quality prospective randomized double-blinded controlled multicenter trials are necessary to be able to evaluate useful applications, expense and cost-efficiency of HBOT for burn care.

Keywords Plastic surgery · Reconstructive surgery · Thermal injury · Carbon monoxide · Review

Introduction

The estimated annual incidence of severe burn injuries in Europe in 2010 was between 0.2 and 2.9/10,000 inhabitants, with 50% of patients younger than 16 years and an overall mortality between 1.4% and 18% [1]. While a decrease in burn incidence and severity as well as mortality and length of hospital stay has been observed in very high to medium high income countries due to burn prevention [2], the overall medical treatment of burn injuries has not been revolutionized in the last few years. Hyperbaric oxygen therapy (HBOT) was introduced for the treatment of thermal injuries in 1965 [3], and was repeatedly expected to be a game changer in burn wound treatment because of its beneficial effects on wound healing and recovery through revascularization, edema reduction, and immune response [4–6]. In addition to thermal injuries patients often suffer concomitant carbon monoxide (CO) poisoning, which needs immediate treatment with 100% normobaric oxygen. Exposure to CO is associated with a wide spectrum of neurological sequelae (e.g. memory loss, affective incontinence, concentration problems) which occur immediately or after a delay and can persist long after the toxic exposure [7, 8]. Neurological sequelae lasting more than 4 weeks and can be observed in 25–50% of patients who suffered loss of consciousness or blood carboxyhemoglobin levels greater than 25%. In severe CO poisoning or if patients have lost consciousness, HBOT is regarded a recommendable treatment option [9]. In defiance of the observed benefits for

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burn wounds and CO poisoning in animal models and some randomized controlled trials there is an ongoing controversy regarding its cost effectiveness [10] and its use and indications [11–15]. Although a huge amount of studies from the last decade tried to evaluate the evidence and efficacy of HBOT in burn care, only very few featured an evidence-based study design. Clear indications for HBOT and its efficiency are still widely unknown to most physicians involved in the treatment of burn patients. Besides a multitude of studies supporting the use of HBOT for various medical conditions which often have few alternative treatment options with similar evidence, reasonable scepticism towards the efficacy of HBOT is present as well and expressed in the literature [16–18].

The purpose of this review is to educate readers on current treatment indications and to evaluate recent publications related, including systematic reviews of the Cochrane Collaboration [15, 19] and meta-analyses as well as proposals of the European Consensus Conference on Hyperbaric Medicine (ECCHM) [20]. The review focuses on an up to date synopsis of the presently available evidence-based data on HBOT in burn care, to elaborate its use in acute thermal injury and carbon monoxide intoxication.

Material and methods

The sources for this review were gathered by searching PubMed, MEDLINE and Google Scholar for randomized controlled trials, systematic reviews and meta-analysis on HBOT in any time frame. Additional references were obtained from a search of the Cochrane Library, existing systematic evidence-based reviews, and existing reference lists. The information was compared and discussed to generate an up to date conclusion regarding the current standpoint of offering HBOT in burn care for patients suffering from thermal injury as well as concomitant CO intoxication.

History of HBOT

Compressed air as a medical treatment was first utilized by the British physician Nathaniel Henshaw through an air-tight pressure chamber in 1662 [21]. After the discovery of oxygen by John Priestly in 1775 and further interest in its therapeutic use, oxygen toxicity was described by French physicians Lavoisir and Seguin in 1789 which slowed down its use in the medical field at first; however, through the understanding of oxygen toxicity which was investigated by Paul Bert in 1878 and in a review by Arntzenius in 1887 the interest in medical HBOT increased once more, which led to the installation of the first hyperbaric chambers in North America [22]. In 1917 Bernhard and Heinrich Dräger first successfully applied pressured air for the treatment of decompression sickness after diving accidents, which was later confirmed and described by Shaw and Behnke in 1937 [23]. Later in 1956, the Dutch cardiac surgeon Boerema reported the aid of pressurized oxygen in cardiopulmonary surgery [24] and in 1961 one of his colleagues Willem Brummelkamp described the inhibition of anaerobic infection under HBOT [25]. The treatment of thermal injuries was first described by Japanese thoracic surgeon Wada in 1966, who observed improved healing tendency in burn wounds after the application of HBOT for CO poisoning [3]. Nowadays, HBOT is utilized in the treatment of a broad spectrum of numerous other medical conditions including open fractures and crush injuries, osteomyelitis, sensorineural hearing loss and rheumatological conditions, although the precise mechanism of action of HBO and its effect on the individual medical condition treated is still not fully understood.

Mechanism of HBOT

It has been demonstrated that HBOT is able to increase the amount of reactive oxygen and nitrogen species [26], which represent important signaling molecules in the generation pathway of a variety of growth factors, cytokines and hormones [27, 28]. Through these mechanisms, alterations of hemoxygenase-1, hypoxia-inducing factor-1, heat shock proteins, and integrin, a reduction of inflammation is triggered and vascular endothelial growth factor inducing neovascularization is synthesized [4]. Other observed effects anticipated through HBOT especially in burned tissue are edema reduction [6], restoration and preservation of microcirculation and angiogenesis [5] as well as increased white cell killing [29]. Simultaneously, with its multilayered induction of wound healing, promotion of fibroplasia, and re-epithelialization take place [30].

Effects on wound healing are triggered by a hyperoxic state of tissues under HBOT. Since hyperoxic tissues do not dilate, subsequent edema reduction and secondary injury are avoided. Higher oxygen concentrations furthermore inhibit the formation of superoxides by neutrophils, which prevent inflammation and further tissue injury [31]. Fibroblasts require oxygen while forming collagen and performing angiogenesis. Tissues with higher oxygen saturation show faster healing through readily available oxygen needed for collagen synthesis. Accelerated angiogenesis further improves nutrient delivery to injured tissues, allowing improved recovery [32]. Another beneficial effect of HBOT is its indirect avoidance of reperfusion injury. In reperfusion injury neutrophils adhere to hypoxic vessels and cause vasoconstriction through release of free radicals and proteases. The use of HBOT has been shown to inhibit neutrophil adherence to damaged vessels and ease postischemic vasoconstriction and subsequent tissue disruption [33]. All these effects are triggered when 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA) is therapeutically administered through respiration in

a pressurized airtight chamber. This results in an increased partial pressure and subsequent oxygen delivery to tissues. Thereby pressure conducted between 1.5 and 3.0 ATA for periods between 60 and 120 min in one or more treatment sessions per day subsequently increases the arterial pO_2 to 1500–2100 mm Hg at the pressure equivalent of 33–66 ft (≙10–20 m) of sea water (≙2–3 ATA). This then again forces up to 6.8 vol.% of oxygen into solution which maintains tissue viability, even in the absence of hemoglobin [4, 24].

Side effects of HBOT are rare and most often not severe [34]. The most common side effects represent moderate otic barotrauma which can occur in up to 10% of patients, or other pressure-related changes affecting air filled organs, such as the lungs, ear drums, or sinuses which is why lower partial pressures are generally preferred. A very rarely observed side effect with a described incidence of 1:10,000–50,000 patients, is central nervous system oxygen toxicity which manifests as a self-limiting grand mal seizure [35]. Myopia which is usually reversible [36], as well as a reduction of blood glucose in diabetic patients has also been reported by patients undergoing prolonged treatment courses [37]. A relative contraindication for HBOT is chronic obstructive pulmonary disease, since air trapping and pulmonary overpressurization could lead to pneumothorax and arterial gas embolism [38, 39].

Indications for HBOT

At present there are only few randomized, controlled clinical trials available on the use of HBOT. Many of its widely accepted applications are based on experimental animal models and clinical observations [40]. A regular evidence-based evaluation of the current literature is performed by the Undersea and Hyperbaric Medicine Society (UHMS) and a list of indications is reported every few years (https://www.uhms.org/resources/hbo-indications.html). Based on the UHMS report, in the meantime 13 indications for HBOT were approved by the U.S. Food and Drug Administration (FDA) (Table 1).

In addition, the European Consensus Conference on Hyperbaric Medicine (ECCHM) performs a regular revision of the list of accepted indications for HBOT based on a thorough review of the most recent and best available research and evidence-based medicine by selected experts. Their most recent Consensus Conference was held in April 2016.

Methodology of the ECCHM

The ECCHM uses evidence-based medical approaches to evaluate and interpret the recently published literature on HBOT. The modified GRADE system [41] for evidence analysis together with the DELPHI system [42] for consensus evaluation are applied. Indications for HBOT were then divided by the ECCHM as follows: type 1, where HBOT is strongly indicated as a primary treatment method, as it is supported by sufficiently strong evidence; type 2, where HBOT is suggested as it is supported by acceptable levels of evidence; type 3, where HBOT can be considered as a possible/optional measure, but it is not yet supported by sufficiently strong evidence. Furthermore, for each type, three levels of evidence were considered by the ECCHM: A) when the number of randomized controlled trials (RCT) is considered sufficient; B) when there are some RCT studies in favor of the indication and there is ample expert consensus and C) when the conditions do not enable proper RCT studies but there is ample and international expert consensus.

Table 1 Indications for HBOT approved by the U.S. Food and Drug Agency (FDA)

FDA approved general conditions for HBOT
Decompression illness
Carbon monoxide poisoning
Air/gas embolism
Chronic refractory osteomyelitis
Clostridial myositis and myonecrosis
Exceptional blood loss anemia
Necrotizing soft-tissue infections
FDA approved wound conditions for HBOT
Burns/thermal injury
Compromised (ischemic) skin grafts and flaps
Crush injury, compartment syndrome, traumatic ischemia
Late radiation tissue injury (soft tissue and bone)
HBOT hyperbaric oxygen therapy

Thermal injuries and burns

Experimental studies

Beneficial effects for thermal injury treatment have been demonstrated in various experimental settings [43, 44] and more recent studies support these findings. A recent experimental study by Hatibie et al. concluded that wound healing in second-degree burns was improved in rabbits by an increase in inflammatory cell migration and re-epithelialization [45]. Selçuk et al. observed accelerated healing by a reduction of scar formation in a rat burn model [46]. Dinar et al. investigated the influence of HBOT on fibrovascular ingrowth in porous polyethylene in healthy versus vascularly compromised burn scar tissue. An enhanced biointegration in hypoxic burn scar tissues via improved collagen synthesis and neovascularization, as opposed to delayed tissue ingrowth in normal healthy tissue was observed [47]. In another rat model, Türkaslan et al. were able to demonstrate that HBOT can stop progression of the zone of stasis to necrosis in the first 24 h after burn injury, which is believed to prevent progression of second-degree burns into third-degree burns [48]. Additionally, Akin was able to observe reduced bacterial translocation

and decreased endogenous bacterial overgrowth in rats treated with HBOT after 30% second-degree burn injury, which is believed to reduce postburn sepsis and multiorgan failure [49].

Clinical experience

Recent studies by Jones et al. focused on the preparation of HBOT treatment guidelines for foot burns in diabetic patients [50, 51]. Since it is difficult to distinguish which patient benefits most and at what time treatment is indicated, they used transcutaneous oxygen measurement (TCOM) to verify local oxygen delivery and estimate wound healing probability [52, 53], which is accepted in the treatment of diabetic foot ulcers, but remains controversial for the evaluation of microcirculation in thermal injuries. Jones et al. assumed TCOM levels between 40 and 50 mm Hg were adequate for normal wound healing [50, 51], and indicated HBOT and vascular studies in cases of absent wound healing [50, 51].

Findings from Jones et al. demonstrated that in cases where $TcPO_2$ was less than 40 mm Hg, a normobaric oxygen challenge was obtained by having the patient breathe 100% O_2 and remeasuring the transcutaneous oxygen pressure ($TcPO_2$) [55]. A pressure >300 mm Hg was estimated to indicate uncompromised arterial flow and unimpaired wound healing ability, while patients with <300 mm Hg and >100mHg levels were estimated to benefit from HBOT [56]. While the retrospective methodology together with the relatively small sample size ($n=22$), resulted in a low statistical power the preliminary results suggest continued investigations of TCOM and HBOT. Although numerous experimental investigations demonstrated HBOT-related benefits, clinical studies were not able to verify the value of HBOT in thermal injury treatment so far. A Cochrane review which tried to find an answer to the questions if mortality and morbidity, healing time, scarring, and number of surgeries as well as fluid requirement after thermal burns can be reduced by HBOT was conducted in 2004. In this thorough review 22 studies were excluded due to poor methodology and insufficient validity of the analysis and found only two small randomized controlled trial with promising results [57, 58], concluding that there is insufficient evidence to refute or support the routine use of HBOT for burn wound treatment [15].

A type IIC indication for HBOT in the treatment of second-degree burn wounds >20% total body surface area was reported by the ECCHM in their most recent report [20]; therefore, HBOT is strongly indicated as an adjunctive primary treatment method, as it is supported by acceptable levels of evidence. An equally high recommendation for its use is found in the setting of decompression illness. The ECCHMs grading is, however, based on the fact that thermal injuries often do not allow proper randomized controlled trials due to heterogeneity. Therefore, the ECCHM grading represents an adjunctive treatment recommendation only.

Treatment of carbon monoxide poisoning

Experimental studies

Besides the ability of HBOT to increase dissolved oxygen blood levels to facilitate faster CO elimination [59–61], the inhibition of lipid peroxidation in the brain [62], and preservation of ATP levels in CO exposed tissue are believed to be neuroprotective [8, 63].

The use of HBOT has been advocated to be neuroprotective in various models of ischemic brain injury in animal models [40–43]. There is a five-fold increase of CO displacement speed from hemoglobin under 100% normobaric oxygen delivered from a reservoir through a face mask that prevents rebreathing and HBOT is believed to increase the CO elimination process even further [59–61]. Additional beneficial effects of HBOT were demonstrated after cyanide (CN) poisoning complicating CO poisoning. While the binding of CN to cytochrome oxidase (CCO) was thought to be irreversible [64], recent findings suggest a competition between nitric oxide (NO) and CN [65, 66]. High concentrations of NO were able to demonstrate a decreased inhibition of CCO by CN and CO [67, 68]. Since HBOT compared to normobaric oxygen therapy (NBOT) has been shown to increase bioavailability of NO, a beneficial effect during CN poisoning is assumed [69, 70].

Clinical experience

While a decrease of neuropsychiatric sequelae is suggested by the use of HBOT in CO poisoning, an overall mortality reduction could not be demonstrated by any study so far [71, 72]. The present report of the ECCHM states a type IB indication for HBOT in the treatment CO poisoning [20], meaning that HBOT is strongly indicated as the primary treatment method. Sufficiently strong evidence and international expert consensus based on some randomly controlled trials in favor of the indication support this approach. A systematic review from the Cochrane collaboration by Buckley et al. (2005) identified seven randomized controlled trials comparing the use of normobaric oxygen versus HBOT [17].

All studies analyzed were of varying quality and one was excluded because clinical outcomes were not evaluated. Of the remaining 6 trials involving 1361 patients, 2 found a beneficial effect of HBOT with a reduction of neurologic sequelae after CO poisoning at 1 month, while the remaining 4 did not. The pooled random effects of the conducted meta-analysis did not suggest a significant benefit from HBOT (odds ratio, OR for neurological deficits 0.78, 95%CI

0.54–1.12); however, it was pointed out that a significant methodologic and statistical heterogeneity was apparent among the analyzed trials, which is why the results should be interpreted cautiously. Certain shortcomings in design and analysis were observed in all of the involved trials according to Cochrane standards. Based on the overall systematic analysis HBOT cannot be routinely recommended for the treatment of CO poisoning. It is however possible that patients with particularly severe CO poisoning may benefit from the treatment [17].

Besides the lack of clinical evidence there are major practical limitations in offering HBOT to patients suffering from CO poisoning. While the half-life of CO in room air is around 4–5 h, it can be decreased to 40–80 min with administration of 100% normobaric oxygen. The set-up of HBOT however, usually takes up at least 2 h, which excludes its use in the emergency setting [73, 74].

A large quantity of 18 different HBOT protocols for CO poisoning have been found in a survey of North American hyperbaric facilities, with high individual variations of used compression periods. The shortest periods of compression lasted 46 min, whereas the longest lasted up to 3 h, and some of the surveyed centers recommended multiple compressions over several days. None of the protocols proved to be superior or was able to demonstrate improved outcome in CO poisoning [75]. One study comparing one versus two HBOT sessions in comatose patients even found an increase in neurological sequelae in the group with repeated HBOT [76]. It is thus difficult to establish a true benefit-risk ratio of HBOT for CO poisoning with the aim of clinical decision-making since the present study results are conflicting. All together no guidelines for the treatment of CO poisoning can be derived from the current body of literature. Additional research, preferably through multicenter randomized trials are needed to define the role of HBOT in CO poisoning [17, 18].

Synopsis

After four decades of research and multiple clinical trials, the benefit, indications, and cost-effectiveness of HBOT in burn care still delivers conflicting findings [9, 10, 16–18]. The quantity and quality of the evidence on the potential benefits and harms of HBOT in patients with thermal injury and CO poisoning is poor and potential benefits cannot be reliably assumed at this point. The lack of larger controlled trials with adequate methodology and statistical power can be explained by the fact that thermal injuries with concomitant CO poisoning often do not allow proper randomized controlled trials due to the heterogeneity of the injury and patient. An overview of the ECCHM grading and Cochrane study reports is depicted in Table 2.

In addition to the heterogeneity of the studied medical conditions and consequent major challenges to evaluate HBOT in randomized controlled trials, another obstacle for HBOT research is the shortage of adequate funding for sufficiently strongly powered trials [10]. According to Fife et al. the fact that although oxygen is a drug, it is not patentable and therefore does not raise particular interest in industry to properly invest in its research is thought to be one of the causes of inadequate funding for HBOT research [38, 77].

Although opinion is deeply divided on this issue, thanks to recent evidence-based research the promising efficacy and indication of HBOT are slowly being decrypted; however, due to a lack of prospective randomized controlled trials, as well as insufficient funding and general challenges to research HBOT in sufficiently powerful randomized controlled trials, performing evidence-based research in this field is markedly aggravated. Due to the high interindividual variability of burns and chronic wounds these studies are extremely difficult to carry out. At this point however, there is an ongoing need for larger high quality, multicenter prospective randomized double-blinded controlled trials to expand and prove useful applica-

Table 2 Comparison of the preliminary European Consensus Conference on Hyperbaric Medicine (ECCHM) consensus conference grading and Cochrane study reports

Indication type	ECCHM grade	Cochrane
Type I		
Osteoradionecrosis (mandible)	B	Weak evidence
CO intoxication	B	Insufficient evidence
Type II		
Burns (2nd degree >20% TBSA)	C	Insufficient evidence
Diabetic foot ulcer	B	Evident beneficial effect (short-term)
Crush injury without fracture	C	Insufficient evidence
Osteoradionecrosis (other bones)	C	Weak evidence
LRTI (other than cystitis/proctitis)	C	Weak evidence
Type III		
Chronic wound (secondary to systemic process)	B	n/a
LRTI (larynx/CNS)	C	Weak evidence

CO carbon monoxide, *TBSA* total body surface area, *LRTI* late radiation tissue injury, *CNS* central nervous system

tions and evaluate the expense and profit efficiency of HBOT for burn care including thermal injury and CO intoxication.

Conflict of interest L. Weitgasser, G. Ihra, B. Schäfer, K. Markstaller, and C. Radtke hereby officially declare that they have no conflict of interest in any form, financial or other and that the manuscript is original and written to the best of their knowledge and has not been submitted anywhere else.

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