POLISH HYPERBARIC RESEARCH 3(60)2017
Journal of Polish Hyperbaric Medicine and Technology Society

HYPERBARIC OXYGEN THERAPY (HBOT) AS A THERAPEUTIC OPTION FOR PATIENTS WITH ATOPIC DERMATITIS (AD) – OWN EXPERIENCES AND LITERATURE REVIEW

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ABSTRACT

The paper discusses the treatment results of ten patients with severe atopic dermatitis (AD) who did not respond to standard pharmacotherapy and underwent hyperbaric oxygen therapy (HBOT). Each patient was subject to 10 oxygen exposures at pO_2 2.5 ATA (~ 250 kPa) with the duration time of 60 minutes. In the period of implementation of the hyperbaric procedures the general treatment plan was suspended for all patients while maintaining typical local treatment. Clinical evaluation was performed in the study group as well as determination of levels of immunoglobulins: IgA, IgG, IgM and IgE and C3 and C4 complement.
All patients indicated clinical improvement and a decreased IgE immunoglobulin and complement C3 level upon the completion of the exposure cycle.
Taking into account the authors' own observations and data from literature, an overall improvement in the clinical status and a decrease in the level of immunoglobulin E and C3 complement following a cycle of exposures may be indicative of an immunomodulating HBOT effect on AD, whereas hyperbaric oxygenation may constitute a therapeutic option for some patients with AD, especially those exhibiting a poor response to standard treatment.
Keywords: atopic dermatitis, HBOT, immunoglobulins, IgE, complement, immunomodulation.

ARTICLE INFO

PolHypRes 2017 Vol. 60 Issue 3 pp. 27 - 36
ISSN: 1734-7009 **eISSN:** 2084-0535
DOI: 10.1515/phr-2017-00012
Pages: 10, figures: 0, tables: 1
page www of the periodical: www.phr.net.pl

Publisher
Polish Hyperbaric Medicine and Technology Society

Original article

Submission date: 13.12.2011r
Acceptance for print: 5.07.2017r.

INTRODUCTION

The use of hyperbaric oxygen therapy procedures has, for many years, occupied a well-established position in medicine as well as evoked continuous interest in researchers. While currently valid consensuses, based on verified data in the methodology referred to as Evidence Based Medicine (EBM), provide an unequivocal systematisation of the possibilities of effective treatment of particular groups of diseases and/or conditions with the use of hyperbaric oxygenation (HBOT) [1], researchers are still exploring new possibilities for the practical application of HBOT procedures.

The conditions for which hyperbaric oxygenation treatment has been recommended for years include decompression sickness, gas embolism, carbon monoxide poisoning, infections caused by anaerobes (or mixed flora), diabetic foot and certain slow healing wounds, and recently also sudden neurosensory deafness [1,2]. In the case of many other conditions, the indications for HBOT can be defined as relative. Moreover, there are attempts to use oxygen hyperbaric therapy to treat less obvious groups of diseases. By analysing the available literature, we may also find publications concerned with the effect of HBOT on the immune system and the use of hyperbaric oxygenation to treat atopic dermatitis (AD), some of which originate in Poland [3,4,5,6,7,8,9,10,11].

Atopic dermatitis (AD) is chronic inflammatory skin disease with periods of exacerbation and remission accompanied by persistent and recurrent pruritus and lichenification of the skin [12,13]. The disease is caused by a genetically determined, abnormal immune response to an antigen/antigens (even in low doses), resulting in an excessive production of specific IgE antibodies, and after binding of the antigen with IgE and its "demonstration" to helper lymphocytes T – a proliferation of T_{H2} lymphocytes secreting proinflammatory cytokines leading in consequence to subjective symptoms (pruritus) and cutaneous lesions of varying advancement [8,11,14]. It is estimated that the disease can affect up to 20% of the population. AD onset usually occurs in the period of infancy, however this is not the rule. In about 40% of children, the disease recedes with age, while in other patients recurrences and/or exacerbations occur during adulthood.

The treatment of atopic dermatitis involves both causal and symptomatic treatment. Causal treatment is based on the elimination of specific antigens, which are known to cause symptoms, from the patient's environment, as well as desensitisation (if possible). Symptomatic treatment involves the use of calcineurin inhibitors – pimecrolimus and tacrolimus (topical), corticosteroids (both topical and general – particularly during exacerbations), antihistamines, photochemotherapy and skin care treatments, and, in severe or refractory cases, also such immunosuppressive drugs as cyclosporine and methotrexate (general). More recently, AD therapy has started to be enhanced with the so-called biological treatment – the main potential is seen in monoclonal antibodies such as omalizumab and dupilumab, as well as mycophenolate mofetil [12,13].

The authors' own clinical observations from previous years indicate a beneficial effect of HBOT on the course and outcome of treatment in some AD cases [7]. mofetylu [12,13].

MATERIAL AND METHODS

The paper demonstrates the results (collected during previous years) of hyperbaric oxygen therapy in ten patients with severe atopic dermatitis, who were untreatable with the then available pharmacological treatments. The discussed treatment group consisted of 5 women and 5 men, aged 18 to 44, admitted to HBOT according to the accepted standards (no contraindications for hyperbaric exposures, normal barofunction prior to each exposure).

All qualified patients were subject to "Skin prick" allergy tests, clinical evaluation (general and topical) regarding the severity of AD symptoms, as well as the determination of class A, G, M and E immunoglobulin levels and C3 and C4 components of complement in blood serum. Laboratory tests were performed twice on each patient, i.e. before and after the cycle of HBOT exposures (Table 1). Laboratory tests were carried out in according to principles of laboratory diagnostics at that time.

Prior to the commencement of HBOT exposures, in addition to topical treatment all patients were treated with oral prednisone (3 patients), cyclosporin (4 patients) and methotrexate (3 patients). All 10 patients discontinued general treatment after the start of hyperbaric oxygenation, however they were advised to continue using personally matched topical therapy based on emollients and steroid ointments available on the market. Antihistaminics (I and II generation) and/or hydroxyzine were also permitted in order to help reduce the feeling of itching.

The implemented treatment protocol in a hyperbaric chamber involved patient compression in air atmosphere to a depth equivalent off $15mH_2O$ at an individually tolerated rate, however not faster than $6mH_2O$/min, after which the patient assumed a lying position and started breathing with pure oxygen at the pressure of 2.5 ATA (~250kPa) for 60 minutes from an inhaler provided inside the chamber. At the end of a 1-hour oxygen inhalation in hyperbaric conditions, each participant switched to breathing with air from the atmosphere of the hyperbaric chamber for 3-5 minutes, in a sitting position, which was followed by decompression to the atmospheric pressure at the rate of $5mH_2O$/min. The treatment cycle for each patient included 10 hyperbaric oxygen exposures: 5 exposures per week for 2 consecutive weeks.

RESEARCH RESULTS AND DISCUSSION

In 9 of the 10 patients who, due to a failure to respond to pharmacological treatments in the control of their AD symptoms, had qualified to undergo HBOT exposures,, the results of the "Skin prick" allergy tests showed: allergy to house dust mites – 5 patients, allergy to grass and cereal pollen – 3 patients, and allergy to tree pollen – 1 patient.

Despite the discontinuation of oral agents during hyperbaric oxygenation treatment, all 10 patients showed a significant local improvement in terms of the dermatological condition (as assessed by a dermatologist who previously referred those patients for treatment with hyperbaric exposures), whereas the patients themselves reported a reduction in the experienced itch. Such good clinical effects were achieved despite the fact that during the implementation of the assumed HBOT procedure

patients were systematically using only topical treatment – i.e. emollients and in some cases (6 patients) also steroid ointments, periodically for several days. All patients undergoing treatment unanimously declared a reduction in their use of oral antipruritic drugs, i.e. antihistaminics and/or hydroxyzine.

When it comes to the assessed laboratory parameters, the cycle of hyperbaric exposures demonstrated an observable downward trend in the absolute values of all examined parameters, with the exception of 4 individual assays (in 4 different patients) of an opposite trend – all of them concerning immunoglobulin levels in patients' serum: IgG - 1 assay, IgA - 1 assay and IgM - 2 assays.

Due to the small sample size and a significant range of values for some of the tests – especially IgE levels, which often differed between patients by 2 orders of magnitude (vide: patient no. 1 vs. patient no. 3), the authors decided to withdraw statistical evaluation of test results and changes, and instead to focus on descriptive analysis. As can be easily seen from a simple analysis of data presented in the table below, the concentrations of immunoglobulins: IgG, IgA and IgM as well as C4 complement component in the serum were not altered, which could raise a suspicion regarding the significance. The situation with IgE and complement C3 complement component in the serum is quite different, where – in the case of a sufficiently large sample – a potential statistical significance could be expected (Tab. 1).

Tab. 1

The comparison of results of test parameters before vs. after HBOT cycle.

Patient no.	Age / Sex [years] / [F/M]	BOT	Immunoglobulin level [mg/dl]				Complement level [mg/dl]	
			IgG	IgA	IgM	IgE	C3	C4
1.	22 / K	before	1500	280	145	250	210	40,1
		after	1300	270	160	210	150	33,2
2.	35 / K	before	1350	250	180	4510	280	34,7
		after	1100	230	150	3100	220	28,2
3.	19 / K	before	1750	140	249	40210	370	28,6
		after	1400	180	210	35400	180	23,8
4.	40 / K	before	1830	240	166	2300	240	32,5
		after	1520	210	140	1840	180	27,4
5.	26 / K	before	1100	250	170	1200	240	32,8
		after	900	216	154	950	130	29,3
6.	18 / M	before	1850	275	230	4200	320	38,8
		after	1700	240	190	3350	260	34,4
7.	39 / M	before	1550	240	192	3230	190	36,5
		after	1700	220	160	3050	160	31,2
8.	44 / M	before	1840	250	188	19270	150	37,5
		after	1620	190	230	15300	120	33,6
9.	24 / M	before	1720	310	130	1640	230	29,5
		after	1400	280	120	1320	190	25,4
10.	37 / M	before	1830	180	210	1330	180	27,2
		after	1500	150	190	1030	130	22,1
Change [% of output value]			83,6	87,9	86,4	81,1	72,8	85,2

As mentioned in the introduction, previous own clinical observations indicated a beneficial effect of HBOT on the course and effects of AD treatment [7]. Similarly, currently presented results indicate both a beneficial therapeutic effect, manifested by a subjective and objective improvement of the clinical condition of the patients, as well as an inhibitory effect on the dynamics of changes in the tested laboratory parameters, particularly immunoglobulin E and C3 complement component. Furthermore, these observations are consistent with the findings of other researchers dealing with the use of hyperbaric oxygenation as a therapeutic option for other groups of diseases associated with an immune activation and inflammatory cascade [11,15,16,17,18,19,20,21].

The downward trend in all parameters tested after the exposure cycle may be indicative of a direct effect of HBOT, both on the synthesis of these specific immunity proteins, and the effect of "quenching" of an inflammatory response in the body. What seems to be significant is the applied breathing mix (100% O_2), as well as the hyperbaric exposure parameters, depending on the overpressure generated in the hyperbaric chamber (and thus on the oxygen partial pressure working on the organism) and exposure time [22,23,24].

This results from a comparison of the specific type of hyperbaric exposures, such as HBOT procedures, with exposures implemented for diving purposes where, depending on the composition of a breathing mix (significant concentrations of inert gases – nitrogen and/or helium) and exposure parameters (usually deeper and longer-lasting), we may observe effects of stimulation of the complement system and other proteins involved in the inflammatory cascade, including opsonin immunoglobulins (not IgE). In the case of diving procedures, this effect is predominantly dependent on the stimulation with (micro)bubbles of nitrogen and/or helium desaturating from a diver's organism during decompression [25,26,27,28,29,30].

Already in the 70's it was observed that exposing of experimental animals to hyperbaric oxygenation (HBO) resulted in the inhibition of various types of cellular immune responses such as allograft rejection, and response to foreign protein and blood cells [22,31,32]. Reports from several decades ago pointed to the effect depending on an increased production and release into the bloodstream of endogenous adrenocortical steroids by stimulation of adrenocorticotropic hormone secretion (ACTH) due to

"oxidative stress" conditions accompanying the HBO exposure. However, this view did not survive the time trial as it was found experimentally that the thus induced ejection of renal cortex steroids (mainly cortisone) resulted in too low it's plasma concentrations and is also maintained for too brief a period after the end of an exposure to be able to speak of any clinically significant immunosuppressive effect [34, 35].

Significant progress in determining the nature of an inhibitory effect of hyperbaric oxygenation on the immune system was made in the 90's, due to a number of valuable, strictly targeted experimental works. Japanese researchers [6] noted that HBO significantly lowers the level of anti-DNA IgG antibodies and immunological complexes in patients with systemic lupus erythematosus and inhibits the production of antibodies to sheep erythrocytes in mice previously intraperitoneally immunised with sheep red blood cells. They were the first to put forward the thesis that HBO does not inhibit any specific mechanism but affects the inhibition of the immunological response mechanism, understood as a whole system of responses, and that the said inhibitory effect is related both to T cell and B cell activity.

In general, the effects of HBO are similar to those accomplished with immunosuppressant drugs, leading to a decrease in inflammatory response in the body [4,35], which is achieved by reducing the synthesis of inflammatory mediators such as nitric oxide (NO) [36, 37], prostaglandin E2 (PGE2) [38,39], tumour necrosis factor α (TNF-α), interleukin 1β and 12 (IL-1β, IL-12) and interferon γ (IFN-γ) [9,16,18,23,38,40,41], as well as a reduced expression of cyclooxygenase-type 2 mRNA (COX-2), an enzyme involved in inflammation [42]. In addition to the inhibitory effect on the synthesis of proinflammatory cytokines, the consequence of hyperbaric oxygen therapy is an increased release of anti-inflammatory cytokines such as interleukin 10 (IL-10) [9,43].

As demonstrated on an animal model by Kudchodkar et al., what is extremely important from the point of view of clinical applications, HBOT also reduced pain intensity, which is one of the symptoms associated with an increased inflammatory response [16]. Although specific molecular mechanisms underlying the immunomodulating effects of hyperbaric oxygenation on the human organism have so far only been partially recognised, the observed effects of HBO appear to be related both to an increased oxygen concentration (or its partial pressure), exposure duration, and an effect resulting from increasing pressure in the hyperbaric chamber.

Such a concept was proposed by Saito et al. as early as 1991 [6], which was repeatedly experimentally confirmed over the following decades [17,23,44,45], with some researchers suggesting the possibility of using hyperbaric oxygen therapy in the treatment of autoimmune diseases. [6,7,46,47,48]. Interestingly, one of the studies demonstrated that even an increased ambient pressure alone, without additional oxygenation of the breathing mix or its replacement with O_2 also led to a reduction of TNF-α levels in experimental animals [24].

It is commonly known that HBOT procedures increase the availability of oxygen at the cellular level, however it happens at the expense of an increased synthesis of reactive oxygen species (ROS) in body tissues [2,49,50,51,52,53]. Although traditionally reactive oxygen species are linked with the progression of inflammatory diseases, it is currently known that elevated ROS levels in tissues due to hyperbaric oxygen therapy with simultaneous presence of immunomodulating molecules indoleamine-2,3-dioxygenase (IDO) and hypoxia-inducible factor 1α (HIF-1α), has a key effect on the function and differentiation of T regulatory cells (Tregs) [54,55,56,57].

These cells – depending on current ROS tissue status and expression of one of the regulatory molecules – may differentiate in two directions: $FoxP3^+$ Tregs (in the case of IDO expression) or T_{H17} (in the case of HIF-1α expression), where an advantage of differentiation in one direction results in the simultaneous inhibition of differentiation in the opposite direction [14,54,55,58,59]. These are important observations, considering the studies conducted by Faleo et al., who found that $FoxP3^+$ Tregs may be involved in the mechanism of preventive effect of HBOT in an animal model (NOD mice) of autoimmune diabetes [21].

Other researchers followed the same route, and in 2014 a paper was published by Kim et al. [11] describing the mechanism by which hyperoxygenation has an alleviating effect on the AD course in experimental animals (mice) due to increased ROS levels in the skin (e.g. as a result of HBOT). The Korean researchers noted that an enhanced IDO expression, and a reduced HIF-1α level in skin lesions in mice treated with HBOT, may induce the generation of a Tregs-dependent environment with a balance towards immunosuppression, as demonstrated by a significant advantage of $FoxP3^+$ Tregs in disease-altered tissues and a reduced concentration of pro-inflammatory mediators: interleukin 17A (IL-17A) and INFγ after hyperoxygenation.

Thus, the authors present a view that tissue direction towards immunosuppression may be stimulated by oxygen-dependent molecules and cells (IDO, HIF-1α and Tregs), contributing to the suppression of inflammatory responses in the course of AD – which according to Kim et al. confirms that tissue hyperoxygenation with HBOT can be seen as an alternative therapeutic strategy for AD patients.

At the end, it is worth pointing out the matter of oxygen hyperbaric procedures' safety. As is well known, HBOT is a fairly safe treatment that has been used for many years in various clinical situations. On the other hand, it involves in patients a risk of an occurrence of toxicity symptoms associated with high O_2 partial pressure, often for a long period of time [2,53,60,61]. However, these adverse effects are usually associated with exposure conditions going beyond the borders commonly used for clinical (typically 1.6–2.8 ATA O_2 for 60-90 min, maximum up to 3 ATA and 120 min) during hyperbaric oxygen therapy – hence their risk is low and acceptable [2,60,61,62,63]. Although the essence of HBOT consists in tissue oxygenation, the oxygen stress developing in the body due to an "excess" of ROS in tissues is biochemically reversible and (usually) does not cause undesirable permanent changes if it is kept within the recommended exposure limits [49,50,51,52,64,65,66].

In conclusion, the practical observations of our team from many years ago presented in the discussed work, are still valid, which is best demonstrated by a wide review of available literature on the subject matter of the article.

CONCLUSIONS

The decreasing tendency in all tested parameters following the exposure cycle and related to a general improvement of a clinical condition of patients, in particular the decrease in the levels of immunoglobulin E and C3 complement component, may be indicative of an immunomodulating effect of HBOT on the course of AD. Hyperbaric oxygen therapy can constitute a therapeutic option for some patients with AD, especially those who are less responsive to standard treatment.

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