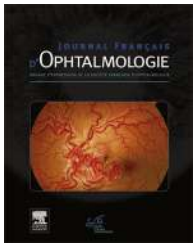
Journal français d'ophtalmologie (2019) xxx, xxx—xxx

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com



ORIGINAL ARTICLE

The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study

Les effets de l'oxygénothérapie hyperbare (OHB) sur la rétinopathie diabétique : une étude préliminaire

A. Maalej[a,*], A. Khallouli[a], R. Choura[a], R. Ben Sassi[b], R. Rannen[a], H. Gharsallah[b]

[a] *Department of ophthalmology, Military hospital of Tunis, Tunis El-manar University, Tunis, Tunisia*
[b] *Department of hyperbaric oxygen therapy, Military hospital of Tunis, Tunis El-manar University, Tunis, Tunisia*

Received 14 March 2019; accepted 3 July 2019

KEYWORDS
Diabetes;
Retinopathy;
Hyperbaric oxygen therapy;
Diabetic foot ulcer;
Macular edema

Summary
Purpose. — The objective of this study was to prospectively assess the effect of hyperbaric oxygen therapy (HBOT) on diabetic retinopathy lesions and macular edema in patients undergoing the treatment for diabetic foot ulcers.
Methods. — We compared two groups: a first group including 25 patients with non-proliferative diabetic retinopathy treated by HBOT for foot ulcers, and a second group (control group) composed of 25 patients with diabetic retinopathy who did not receive HBOT. The HBOT protocol performed for the patients in the first group was: 30 sessions of 90 minutes each at 2.5 ATA with a mean frequency of five sessions per week. All patients had an ophthalmological exam at baseline (visual acuity, intraocular pressure, fundus exam), fundus photography and an OCT exam. A follow-up exam was performed at the conclusion of the HBOT.
Results. — Compared to the control group, patients treated with HBOT showed a regression or stabilization of diabetic retinopathy lesions and a decrease in central macular thickness (CMT).

* Corresponding author.
E-mail address: afefmaalej@yahoo.fr (A. Maalej).

https://doi.org/10.1016/j.jfo.2019.07.005

Conclusion. — Hyperbaric oxygen therapy may improve diabetic retinopathy and diabetic macular edema. This therapy may serve as an adjunctive treatment in the management of retinal ischemia and capillary hyperpermeability in diabetic retinopathy.

MOTS CLÉS
Diabète ;
Rétinopathie ;
Oxygénotherapie hyperbare ;
Pied diabétique ;
Œdème maculaire

Résumé
Objectif. — Évaluer à travers une étude prospective l'effet de l'oxygénothérapie hyperbare (OHB) sur les lésions de rétinopathie diabétique et sur l'œdème maculaire diabétique, chez des patients traités par des séances d'oxygénothérapie hyperbare pour un pied diabétique.
Méthodes. — Deux groupes ont été comparés : le premier groupe comportait 25 patients traités par OHB pour des pieds diabétiques, et chez qui une rétinopathie diabétique non proliférante a été diagnostiquée à l'examen du fond de l'œil. Le groupe contrôle comportait 25 patients ayant une rétinopathie diabétique mais chez qui aucun traitement par OHB n'a été préconisé. Le protocole d'OHB réalisé chez les patients du premier groupe était comme suit : 30 sessions de 90 minutes chacune à 2,5 ATA avec une moyenne de cinq séances par semaine. Tous les patients ont eu un examen ophtalmologique initial (Mesure de l'acuité visuelle et de la pression intra-oculaire, examen du FO), une photographie du FO ainsi qu'un examen OCT. Un examen de contrôle a été fait à la fin de l'OHB.
Résultats. — Comparés au groupe contrôle, les patients traités par OHB ont eu une régression ou une stabilisation de leur rétinopathie diabétique. Une réduction de l'épaisseur maculaire centrale (EMC) a également été notée après OHB.
Conclusion. — L'oxygénothérapie hyperbare semble améliorer les lésions de rétinopathie diabétique et l'œdème maculaire diabétique. Ce traitement peut constituer un moyen thérapeutique complémentaire pour l'ischémie rétinienne et l'hyperperméabilité capillaire au cours de la rétinopathie diabétique.

Background

Like most countries, diabetes is a major health problem in Tunisia. Diabetic foot ulcer is a serious complication and is the main cause of non-traumatic amputation. Hyperbaric oxygen therapy (HBOT) is an adjunctive therapeutic method usually used for the treatment of diabetic foot ulcers in patients having poorly controlled diabetes and often severe diabetic retinopathy [1]. Initially performed to improve foot oxygenation, HBOT can have a good effect on retinal diabetic microangiopathy [2].

Purpose

We aimed to assess the effect of HBOT on diabetic retinopathy lesions and macular edema in patients who had this treatment initially for diabetic foot ulcers.

Methods

Enrolment of study population

We performed a prospective non-randomised study between March and June 2018. We received in the department of ophthalmology, all diabetic patients undergoing HBOT for foot ulcers in order to systematically detect a diabetic retinopathy.

Patients were divided into two groups:

- the first group (HBOT+) included 25 patients treated by HBOT for diabetic foot ulcers. The fundus exam noted a non-proliferative diabetic retinopathy referring to the ETDRS classification system [3];
- the second group (HBOT−) was composed of 25 diabetic patients with a non-proliferative diabetic retinopathy on the fundus exam, but without any foot ulcer nor any indication for HBOT.

An informed consent was obtained for all patients included in the study.

Data collection

All patients had undergone a full ophthalmological exam at baseline: best corrected visual acuity (BCVA), non-contact intra-ocular pressure measurement (IOP), fundus exam and photography, macular SD-OCT exam. A second examination was done six weeks later, corresponding to the end of the HBOT.

Please cite this article in press as: Maalej A, et al. The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study. J Fr Ophtalmol (2019), https://doi.org/10.1016/j.jfo.2019.07.005

Table 1 General characteristics of patients in both groups.

	Group 1 (HBOT +)		Group 2 (HBOT −)		*P*
Mean age	58 years		61 years		0.567
Sex ratio	1.2		1.4		0.545
mean HbA1c	8.9		8.4		0.824
DR stage	Mild	12	Mild	13	0.468
	Moderate	9	Moderate	10	
	Severe	4	Severe	2	

HBOT protocol

The HBOT protocol indicated in case of diabetic foot ulcers is as following: 30 sessions of 90 minutes at 2.5 atmosphere absolute (ATA) with a rate of five sessions per week (one session per day).

Inclusion criteria

We have included:
- male or female between the age of 18 and 85;
- diabetic patients with a non-proliferative diabetic retinopathy on the fundus exam;
- patients with diabetic foot ulcers (group 1) or not (group 2).

Non-inclusion criteria

We have not included patients:
- without diabetic retinopathy;
- with proliferative DR needing immediate treatment, already treated DR (by laser or anti-VEGF intravitreal injections);
- with contraindications for HBOT (emphysemia, epilepsy...).

This study adheres to the tenets of Declaration of Helsinki.

Statistical analysis

The comparability of the two groups was assessed using independent-samples *t*-test for quantitative variables and Pearson's Chi^2 test for qualitative variables.

We compared the quantitative data obtained from the first and the final examinations using an independent-samples *t*-test for BCVA and a paired t-test for IOP variation. Changes in the distribution of the stages of DR between enrolment and final control were evaluated using chi-squared test. Central macular thickness (CMT) variation was assessed in each group using a paired *t*-test.

Statistical analysis was performed with SPSS for Windows (SPSS Inc.), with $P < 0.05$ considered as statistically significant.

Results

The two groups compared in our study were matched for the mean age ($P = 0.567$), the sex ratio ($P = 0.545$), the degree of the diabetic control ($P = 0.824$) and the stage of DR at the first examination ($P = 0.468$) (Table 1).

Table 2 Evolution of the BCVA in both groups.

	Mean BCVA	
	At baseline	Final
Group 1 (HBOT +)	0.72	0.83
Group 2 (HBOT −)	0.74	0.69
P	0.473	$P = 0.009$

Table 3 Variation of IOP in both groups.

	Mean IOP (mmHg)		
	At baseline	Final	*P*
Group 1 (HBOT +)	14.8	13.2	< 0.001
Group 2 (HBOT −)	15.6	15.9	0.005

Regarding to visual results, BCVA did not show any statistically significant difference between the two groups at the first examination ($P = 0.473$). However, we noted at the final examination that BCVA was significantly better in the first group (HBOT +) ($P = 0.009$) (Table 2).

All patients underwent a non-contact IOP measurement. In the first group (HBOT +), mean IOP decreased significantly after treatment ($P < 0.001$). Yet in the second group (HBOT −), mean IOP increased significantly ($P = 0.005$) (Table 3).

We compared the distribution of the stages of DR between the first and the final examination. In the first group (HBOT +), we noticed more mild DR (Figs. 1 and 2) and less severe DR at the final examination ($P < 0.001$). In the second group however, the number of severe DR increased from 2 to 4 ($P < 0.001$) (Table 4). This fast progression was observed in two young patients with poorly controlled type 1 diabetes. An adequate care has been taken to prevent a florid diabetic retinopathy.

We also looked at the CMT in all eyes. Treated eyes (HBOT +) showed a significant decrease in the mean CMT measured by SD-OCT after HBOT ($P = 0.006$) (Figs. 3 and 4). In untreated eyes (HBOT −), CMT was significantly higher at the final examination comparing to the initial measure ($P = 0,008$) (Table 5).

Please cite this article in press as: Maalej A, et al. The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study. J Fr Ophtalmol (2019), https://doi.org/10.1016/j.jfo.2019.07.005

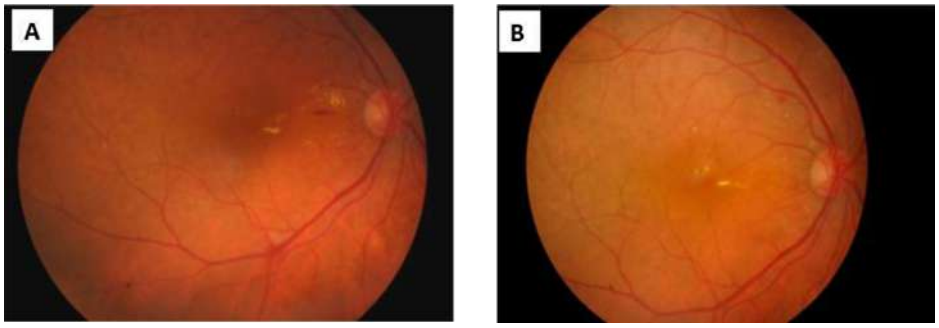


Figure 1. Fundus photography of a 45 year-old man, before (A) and after (B) HBOT: disappearance of retinal hemorrhages and some exudates.

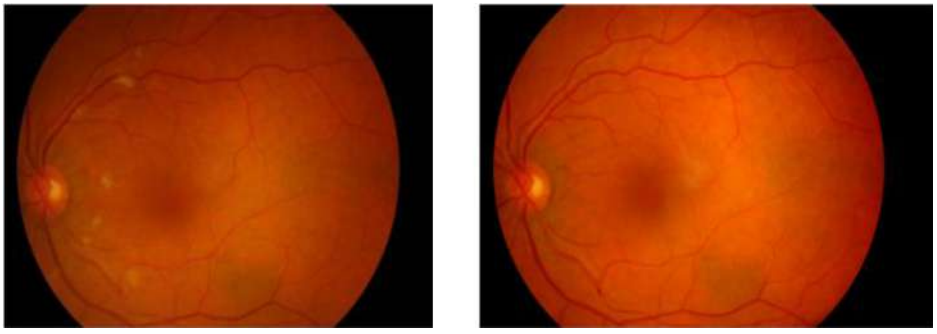


Figure 2. Fundus photography of the left eye of a 52 year-old woman: resolution of cotton wools after HBOT.

Table 4 Stages of DR at baseline and at the final exam.

NPDR	Mild	Moderate	Severe	Total	*P*
Groupe 1 (HBOT+)					
Baseline	12	9	4	25	< 0.001
Final	14	8	3	25	
Groupe 2 (HBOT−)					
Baseline	13	10	2	25	< 0.001
Final	10	11	4	25	

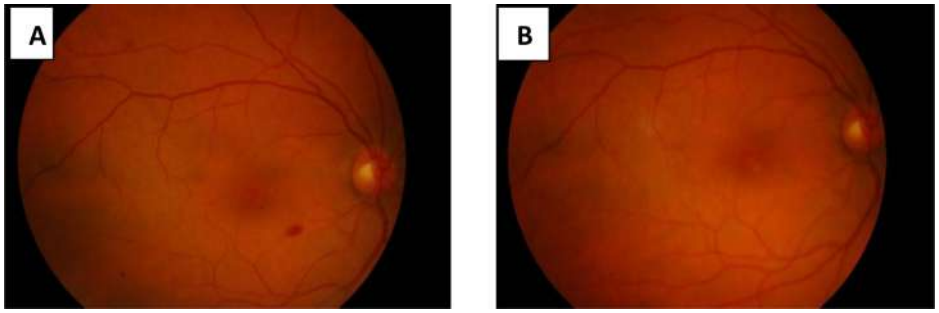


Figure 3. Fundus photography of a 52 year-old woman showing resolution of retinal hemorrhages after HBOT. A. Before treatment, B. after treatment.

Discussion

Diabetic foot ulcers are a serious complication of poorly controlled diabetes. It represents the first cause of non-traumatic amputation. It raises the social costs of diabetes [4]. The consensus conference of hyperbaric oxygen therapy association postulates that diabetic foot ulcers are a confirmed clinical indication for HBOT with a strong agreement [5]. The effect of hyperoxygenation on tissues is performed by an improvement of compromised tissue oxygenation, an antimicrobial action and a promotion of wound healing through stimulating fibroblasts proliferation, collagen synthesis, and neoangiogenesis [1,6].

Please cite this article in press as: Maalej A, et al. The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study. J Fr Ophtalmol (2019), https://doi.org/10.1016/j.jfo.2019.07.005

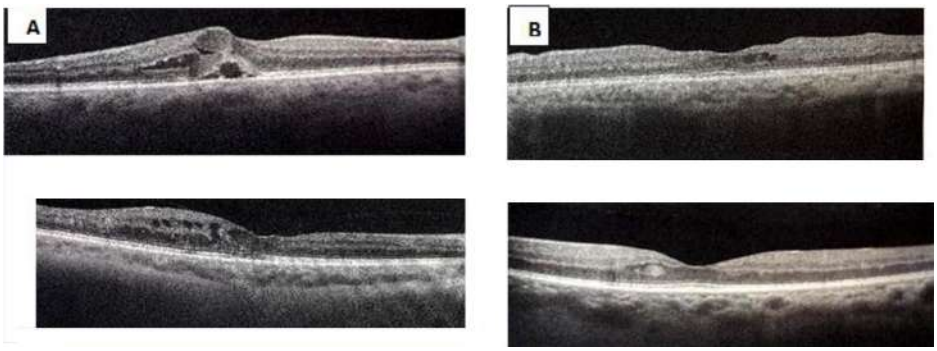


Figure 4. Improvement of the diabetic macular edema after HBOT A. Macular OCT scans before HBOT. B. Macular OCT scans after HBOT.

Table 5 Variation of the central macular thickness (CMT) in both groups.

	MeanCMT		
	At baseline	Final	*P*
Group 1 (HBOT +)	321 μm	272 μm	0.006
Group 2 (HBOT −)	341 μm	352 μm	0.008

HBOT is the best adjunctive therapy to improve healing [1]. The protocol of treatment for diabetic foot ulcers is already established. It comprises 30 sessions of 90 minutes at 2.5 ATA with a rate of five sessions per week (one session per day). The total duration of treatment is six weeks [6].

Diabetic retinopathy is often associated to foot ulcers and must be detected by a systematic ocular exam. Then, it can be treated at time before any complications [7].

The Treatment of ophthalmic disorders is an off label use of HBOT [8–10]. Diabetic retinopathy and cystoid macular edema are considered as potential indications of this treatment [11,12]. Other reported ophthalmological indications are: retinal artery and vein occlusions, anterior segment ischemia, macular degeneration, retinitis pigmentosa and glaucoma [5,6].

Several studies reported a decrease in IOP measurements secondary to HBOT. Yet, the role of HBOT in the management of glaucoma remains debatable [13–15].

HBOT can lead to some side effects such as barotrauma, pulmonary and neurological oxygen toxicity, cataracts, transient reversible myopia (20%) [8,16]. It's necessary to respect contraindications of this treatment in order to avoid complications.

How does HBOT act?

HBOT leads to an increase in the partial pressure of the oxygen in the lungs which increases the oxygen content of the blood and consequently, it induces an increase of the blood flow in the ischemic areas [6].

Oxygen is obviously a determining element for the retina. It plays a primordial role in aerobic glycolysis and in maintaining the homeostasis of the retinal tissues [17].

Studies evaluating HBOT effects on DR are rare. According to experimental evidence, an increase in oxygen availability would cause an improvement in vision [18].

HBOT was reported to be useful in the treatment of diabetic retinopathy; it improves the blood-retinal barrier breakdown. Hence, it can prevent and treat persistent macular edema [2,17].

Conclusion

Hyperbaric oxygen therapy is of growing interest for the treatment of persistent diabetic foot ulcers. It may improve diabetic retinopathy and macular edema.

HBOT may serve as an adjunctive treatment in the management of retinal ischemia and capillary hyperpermeability in diabetic patients. Further large-scale prospective controlled studies are needed to confirm these results. Limits of such a treatment are mainly the availability of the hyperbaric chamber and the cost effectiveness.

Disclosure of interest

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

The authors declare that they have no competing interest.

References

[1] Jira M, El Omri N, Sekkach Y, Mekouar F, Amezyane T. Hyperbaric oxygen therapy in the treatment of diabetic foot: experience in the management of 80 cases at a department of internal medicine. Pan Afr Med J 2018;30:100.
[2] Chen J. The effects of hyperbaric oxygen therapy on diabetic retinopathy. Invest Ophthalmol Vis Sci 2003;44:4017.
[3] Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic colour fundus photographs an extension of the Modified Airlie House Classification: ETDRS report number 10. Ophthalmology 1991;98:786–806.
[4] Reiber GE, Ledoux WR. Epidemiology of diabetic foot ulcers and amputations: evidence for prevention. In: The evidence base for diabetes care. John Wiley & Sons, Ltd; 2003. p. 641–65.
[5] Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on hyperbaric medicine: preliminary report. Diving Hyperb Med 2016;46:122–3.

Please cite this article in press as: Maalej A, et al. The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study. J Fr Ophtalmol (2019), https://doi.org/10.1016/j.jfo.2019.07.005

[6] Bauer P, Berrod JP, Lambert H. Hyperbaric oxygenotherapy: current data. Bull Soc Ophtalmol Fr 1988;88:1417—20.
[7] Hwang DJ, Lee KM, Park MS, Choi SH, Park JI, Cho JH, et al. Association between diabetic foot ulcer and diabetic retinopathy. PLoS ONE 2017;12:e0175270.
[8] De Marigny G, Mouillon. Hyperbaric oxygenotherapy and refraction. Bull Soc Ophtalmol Fr 1971;71:309—12.
[9] Patyal A. Hyperbaric chamber and its ophthalmic applications. Delhi J Ophthalmol 2017;28:41—2.
[10] Gorman D. Oxygen therapy and ophthalmology. Oman J Ophthalmol 2013;6:S5—7.
[11] Xu YN, Huang JG. Hyperbaric oxygen treatment for cystoid macular edema secondary to retinal vein occlusion. Zhonghua Yan KeZaZhi 1991;27:216—8.
[12] Chang Y-H, Chen P-L, Tai M-C, Chen C-H, Lu D-W, Chen J-T. Hyperbaric oxygen therapy ameliorates the blood-retinal barrier breakdown in diabetic retinopathy. Clin Exp Ophthalmol 2006;34:584—9.
[13] Bojić L, Kovacević H, Andrić D, Romanović D, Petri NM. Hyperbaric oxygen dose of choice in the treatment of glaucoma. ArhHig Rada Toksikol 1993;44:239—47.
[14] Bojic L, Racic G, Gosovic S, Kovacevic H. The effect of hyperbaric oxygen breathing on the visual field in glaucoma. Acta Ophthalmol 1993;71:315—9.
[15] Gallin-Cohen PF, Podos SM, Yablonski ME. Oxygen lowers intraocular pressure. Invest Ophthalmol Vis Sci 1980:43—8.
[16] Palmquist BM, Philipson B, Barr PO. Nuclear cataract and myopia during hyperbaric oxygen therapy. Br J Ophthalmol 1984;68:113—7.
[17] Pfoff DS, Thom SR. Preliminary report on the effect of hyperbaric oxygen on cystoid macular edema. J Cataract Refract Surg 1987;13:136—40.
[18] Miyake Y, Awaya S, Takahashi H, Tomita N, Hirano K. Hyperbaric oxygen and acetazolamide improve visual acuity in patients with cystoid macular edema by different mechanisms. Arch Ophthalmol 1993;111:1605—6.

Please cite this article in press as: Maalej A, et al. The effects of hyperbaric oxygen therapy on diabetic retinopathy: A preliminary study. J Fr Ophtalmol (2019), https://doi.org/10.1016/j.jfo.2019.07.005