Hiperbarik Oksijen Tedavisi Sonrası Diyabetik Retinopatide İlerleme ve Maküla Ödeminde Artış Olabilir mi?

Is There Aggravating Effect of Hyperbaric Oxygen Therapy on Diabetic Retinopathy and Macular Edema?

Sezen AKKAYA[1], Fatih Bilgehan KAPLAN[2]

ÖZ

Elli dört yaşında diyabetik hasta polikliniğimize endokrin bölümünden göz dibi muayenesi için yönlendirildi. Muayenesinde en iyi düzeltilmiş görme keskinliği (EİDGK) Snellen eşeli ile sağ gözde 0,3 sol gözde 0,5 olup, göz tansiyonları ve biyomikroskopik muayenesi doğaldı. Fundus muayenesinde her iki gözde orta şiddette proliferatif olmayan diyabetik retinopati bulguları ve diyabetik makula ödemi tespit edildi. Hastaya fundus floresein anjiografi(FFA) çekilmesi planlandı. Hastanın çekilen optik kohorens tomografisinde(OKT) her iki gözde makula kalınlığının artmış, kistoid makula ödemi ve seröz makula dekolmanı mevcuttu. Hastaya her iki göze 3 kez 1 ay ara ile intravitreal anti-VEGF(vasküler endotelyal growth faktör) enjeksiyonu önerildi. Ancak hasta diyabetik ayak nedeniyle önerdiğimiz anti-VEGF tedaviye gelemeyerek bir ay hiperbarik oksijen tedavisi(HBOT) aldı. Hasta HBOT bittikten 10 gün sonra görmesinde hızlı bir düşme olduğunu belirterek polikliniğimize tekrar başvurdu. Muayenesinde görmeleri Snellen eşeli ile sağ gözde 0,1 sol gözde 0,05 olup, her iki gözde makula ödeminde, seröz makula dekolmanında artış ve sol gözde optik disk neovaskülarizasyonu (NVD) gelişerek bu gözün proliferatif faza geçtiği saptandı.

Bu ilerleme hastanın kötü giden diyabet regülasyonu ve intravitreal tedavisini alamaması nedeniyle gerçekleşmiş olabilir. Ancak görmede azalmanın HBOT sırasında değil ama tedavi bitiminden 10 gün sonra görülmesi ve NVD'nin hızlı gelişimi bu durumu sorgulamamıza neden oldu. HBOT bittikten sonra ani oksijen saturasyonu düşmesinin bu duruma katkı sağlamış olabileceği düşüncesindeyiz. HBO tedavisine gönderilen diyabetik hastaların HBOT bitiminden hemen sonra oftalmolojik muayeneden geçirilerek fundus muayenelerinin sıkı takip edilmesi gerektiğini düşünüyoruz. Diyabetik retinopatide olduğu gibi vitreusta artmış VEGF düzeyleri olan tüm hastalarda bu durumun irdelenmesi gerektiği kanaatindeyiz.

Anahtar Kelimeler: Hiperbarik oksijen tedavisi, diyabetik makula ödemi, diyabetik retinopati.

ABSTRACT

A 54-years-old diabetic patient was referred to our clinic for fundus examination. The best corrected visual acuity (BCVA) with Snellen chart was 0.3 and 0.5 in the right and left eyes, respectively. In the fundus examination, moderate non-proliferative diabetic retinopathy (DR) signs and diabetic macular edema (DME) were detected in both eyes. FFA imaging was planned. OCT showed increased macular thickness (CMT) in both eyes, DME and serous macular detachment. Three monthly intravitreal anti-VEGF injection was recommended for both eyes. However, we were unable to treat the patient due to presence of diabetic foot; thus, the patient underwent hyperbaric oxygen therapy (HBOT) over a month. However, the patient presented with accelerated decrease in vision in both eyes 10 day after completion of HBOT. The BCVA was found as 0.1 and 0.05 in the right and left eyes, respectively. In addition, it was found that there was worsening in DME, serous macular detachment in both eyes with optic disc neovascularization (NVD) in the left eye. The disease progression may be due to poor diabetes regulation in the patient and inability to receive intravitreal treatment. However, the fact that there was no loss in visual acuity during HBOT but occurred on day after the completion of HBOT and that NVD was developed in this period should be questioned. We think that the sudden drop in oxygen saturation after the end of HBOT may have contributed to this situation. We believe that this condition should be addressed in all patients with elevated VEGF levels, such as DR.

Key Words: Hyperbaric oxygen therapy, diabetic macular edema, diabetic retinopathy.

1- Uz. Dr., Sağlık Bilimleri Üniversitesi Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Göz Hast., İstanbul, Türkiye

2- Asist. Dr., Sağlık Bilimleri Üniversitesi Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Göz Hast., İstanbul, Türkiye

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Yazışma Adresi / Correspondence Adress:
Sezen AKKAYA
Sağlık Bilimleri Üniversitesi Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Göz Hast., İstanbul, Türkiye

Phone: +90 216 578 3000
E-mail: drsezenakkaya@gmail.com

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is a medical treatment modality provided by breathing patient with 100% oxygen intermittently under ambient pressure exceeding atmospheric pressure (1 atmosphere absolute [ATA]=760 mmHg) in a closed pressure chamber.[1] Hyper-oxy leads dissolution of high amounts of oxygen in the plasma and increased oxygen diffusion distance within tissues. Primary mechanism of action relies on 20-folds increase in plasma oxygen solubility, partial oxygen pressure and oxygen concentration. Thereby, oxygen can be transported to more distal areas and tissue oxygenation can be achieved without need for hemoglobin.[1] HBOT allows increased amount of soluble oxygen in plasma and oxygenation of hypoxic tissues; thus, proliferation of anaerobic bacteria is inhibited; synergistic effect may be achieved with some antibiotics; edema is relieved by vasoconstriction; cytotoxic effect is prevented in carbon monoxide and cyanide poisoning; leukocyte activation is enhanced at wound site; angiogenesis and connective tissue formation are induced at wound site.[1] Major indications are decompression disease, air and gas embolism, carbon monoxide and cyanide poisoning, acute smoke inhalation, gas gangrene, necrotizing infections of soft tissues (subcutaneous tissue, muscle, fascia), conditions with delayed wound healing (diabetic and non-diabetic), chronic refractory osteomyelitis, skin flaps and grafts with potential failure, anoxic encephalopathy, sudden hearing loss and retinal artery occlusion.[2] The major adverse events include barotrauma, central nervous system and pulmonary oxygen toxicity and ocular events. Ocular side effects include transient myopia and cataract formation. Retrolental fibroplasia is a severe complication occurring at premature retina where vascularization is immature. In retrolental fibroplasia, VEGF level is increased with proliferation, representing similarities with diabetic patients.[3] In diabetes mellitus, tissue oxygenation is impaired due to cappillary basal membrane abnormalities. Oxygen level can be increased in ischemic wound tissue by increased diffusion distance in HBO therapy.[4] Hyperbaric oxygen therapy increases vascular endothelial growth factor (VGEF) synthesis in ischemic wound tissue and basic fibroblast growth factor (BFGF) and transforming growth factor-β1 (TGF-ß1) release from human dermal fibroblasts, angiopoetin-2 release from human umbilical vein endothelium and placental growth factor (PGF) release from human mesenchymal stem cells. These growth factors are beneficial in many disorders but they may cause progression of diabetic retinopathy.[5-7] In hyperbaric medium, oxygen stimulates capillary proliferation (angiogenesis), which, in turn, provides support to novel capillary network by increasing collagen synthesis. It facilitates formation of novel capillary network by accelerating mucopolysaccharide synthesis which is major element in vessel formation. This feature contributes to graft/flap preservation and chronic wounds.[8]

Bases on free radical theory, free radicals (superoxide and hydroxyl radical) or peroxides generated as a result increased metabolic events due to hyper-oxy, rather than oxygen molecule itself, are responsible from cellular damage in HBO toxicity. The elevated levels of oxygen forms with higher reactivity leads damage in membrane lipids, nucleic acids and diamino acids, resulting in toxicity symptoms.[9]

CASE REPORT

A 54-years diabetic patient was referred to our clinic for fundoscopy by endocrine department. The patient had type 2 diabetes and was on insulin therapy for 7 years. In most recent laboratory evaluation, HbA1c level was 6.8 mg/dL. In his history, it was found out that the patient underwent toe amputation due to diabetic foot and received no laser photocoagulopathy or intravitreal therapy. In the physical examination, best corrected visual acuity was found as 0.3 in right and 0.5 in left eye by Snellen chart while IOP and slit lamp examination were normal in both eyes. In fundus examination, there was soft exudate, hard exudate and micro-aneurysms in both eyes (Figure 1). In addition, moderate, non-proliferative diabetic retinopathy was detected in both eyes and FFA imaging was planned. The FFA was requested from patient (Figure 2). On optical coherence tomography (OCT),

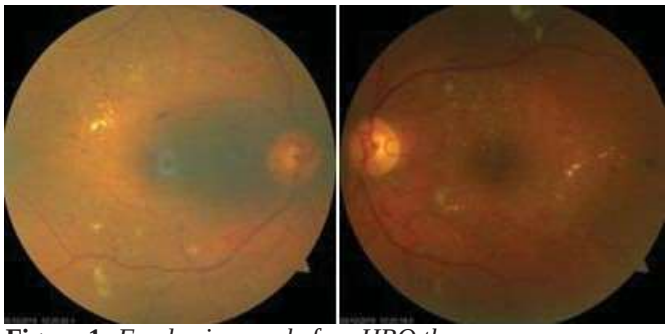

Figure 1: *Fundus images before HBO therapy*

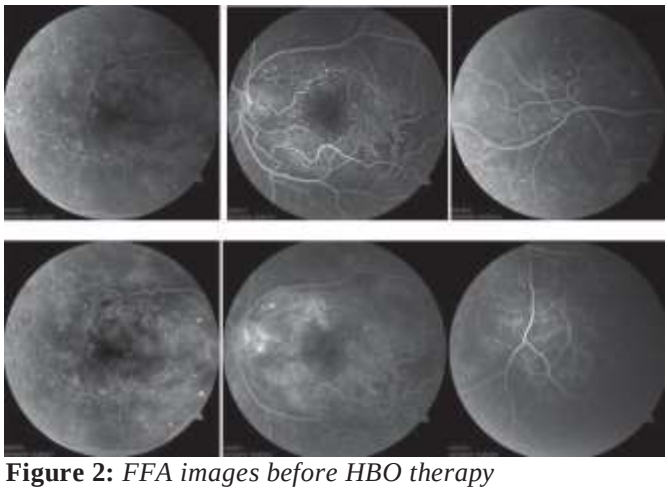

Figure 2: *FFA images before HBO therapy*

there was increased macular thickness in both eyes (as being more prominent in right eye), serous macular detachment and cystoid macular edema (Figure 3). Treatment with 3 monthly intravitreal anti-VGEF injections was recommended to the patient. However, the patient did not attend for treatment. However, the patient presented with acute and severe impairment in vision after 40 days. In the history, it was found out that he was referred to HBO therapy (2 hours per day over 30 days); thus, he failed to receive intravitreal anti-VGEF therapy. In the physical examination, best corrected visual acuity was found as 0.1 in right and 0.05 in left eye by Snellen chart while IOP and slit lamp examination were normal in both eyes. In fundus examination, it was found that exudate formation disappeared after HBO therapy; however, flame-like hemorrhages were developed and there was an arterial embolus on superior temporal artery of left eye. In addition, diabetic macular edema was worsened in both eyes and optic disk neovascularization (NVD) occurred in left eye (Figure 4). The FFA imaging revealed peripheral perfusion defect in both eyes, occasional areas of ischemia and NVD onset in left eye (Figure 5). The retinopathy evolved to proliferative form in left eye. On OCT imaging, it was seen that there was increased reflectivity at inner retinal layers, worsened serous macular detachment and intensified cystoid macular edema after treatment (Figure 6). We planned to administer 3 doses of intravitreal anti-VGEF injection in both eyes and pan-retinal photocoagulation (PRP) in the left eye.

In this case, we aimed to emphasize that there may be progression in retinopathy due to reduced oxygen level following HBO therapy; thus, meticulous fundoscopic follow-up will be appropriate in the patients undergoing HBO therapy.

DISCUSSION

In ophthalmology, HBO therapy is used in sudden loss of vision caused by retinal artery occlusion. The aim of HBO therapy is to maintain retinal oxygenation through choriocapillaris even in the occlusion of central retinal artery that supplies two-third of retina. It may be possible to preserve retinal viability and functions as blood oxygen content and oxygen diffusion will increase proportionally to elevated pressure during HBO therapy. In addition, HBO therapy leads stem cell mobilization via nitric oxide (NO) synthesis. It was found that HBO therapy contributes to restoration of retinal damage by stem cell mobilization in addition to anti-hypoxic effect.[10]

In addition to beneficial effects, HBO therapy may exert negative ocular effects which may vary depending on treatment depth, treatment duration and age. It is well-known that progressive myopia develops within 2-4 weeks in patients undergoing HBO therapy due to various indications, particularly in those aged>50 years. It is though that the variations observed in refraction results from shape of lens

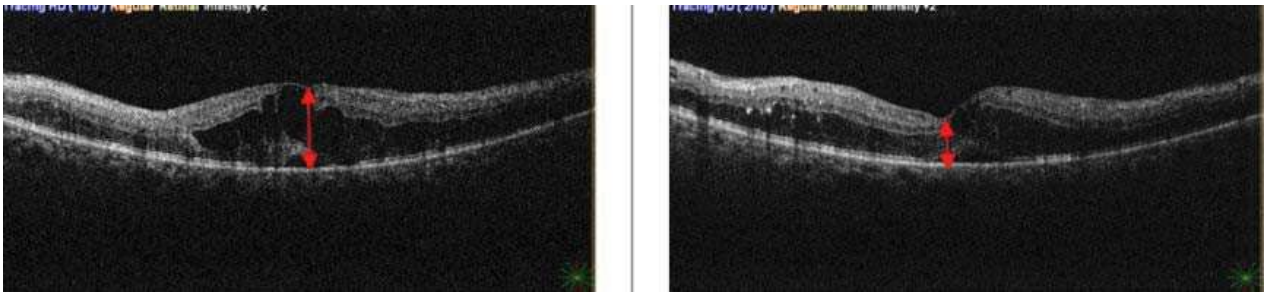

Figure 3: *Right eye before HBO therapy OCT: 598um Left Eye before HBO therapy OCT: 390um.*

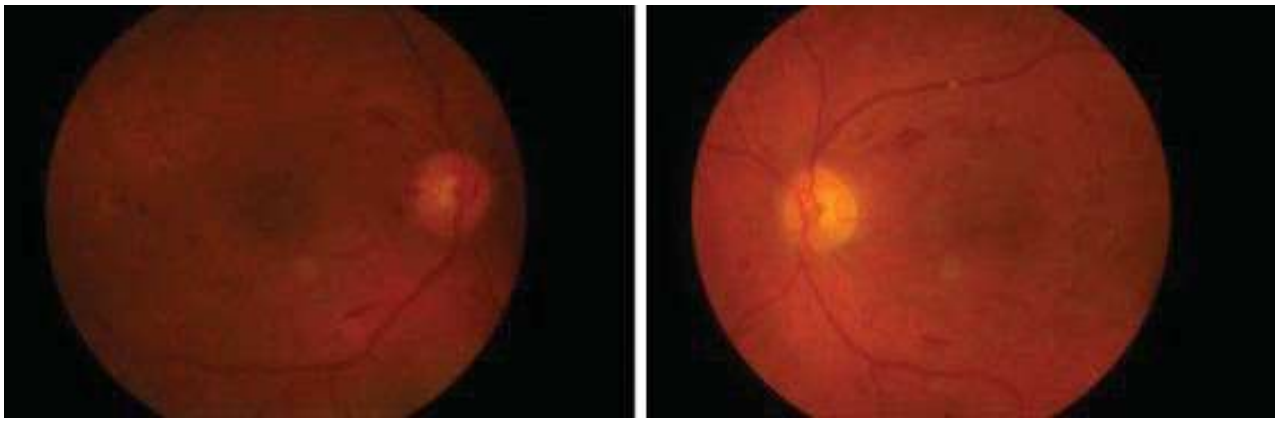

Figure 4: *Fundus images after HBO therapy.*

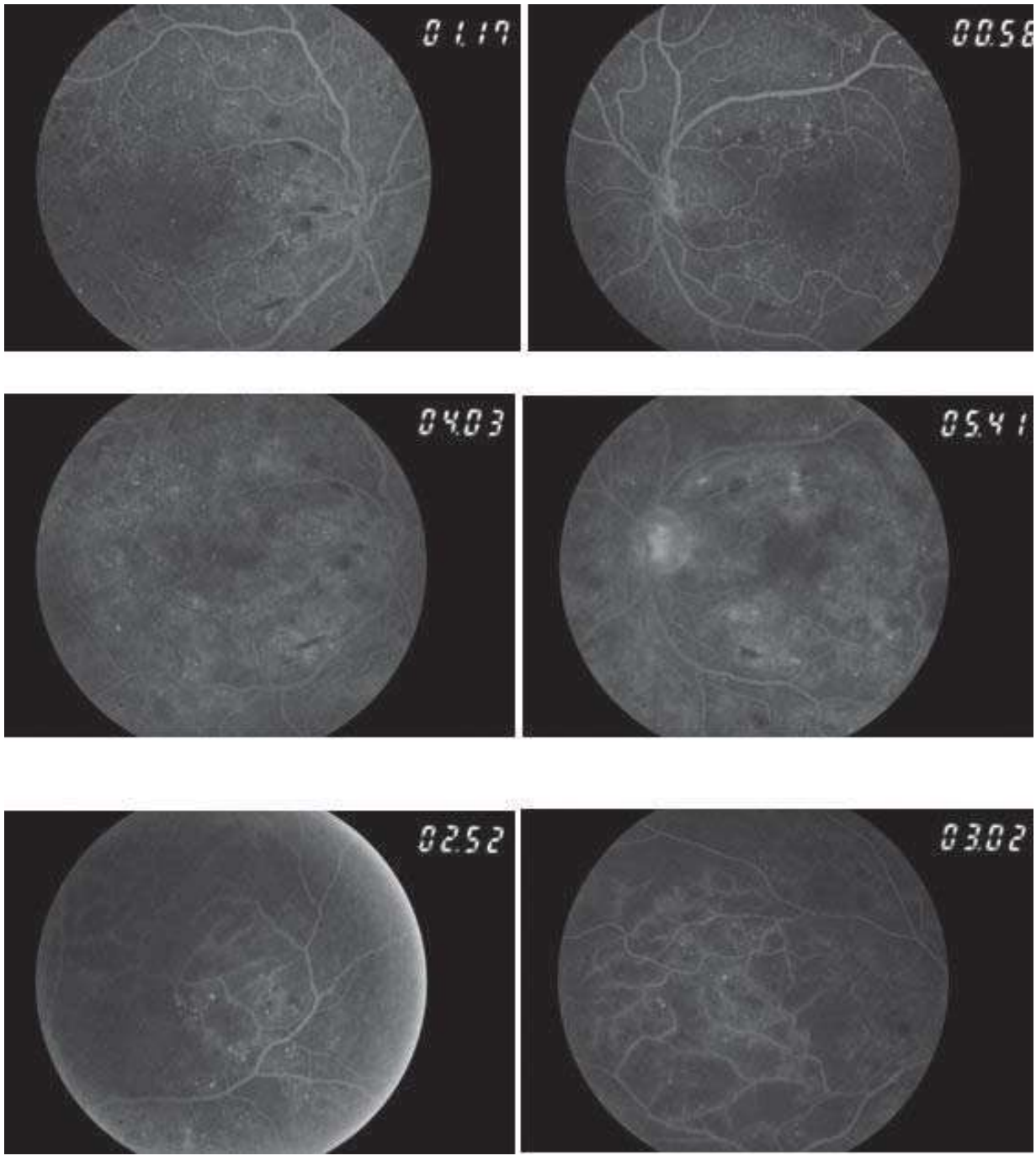

Figure 5: *FFA after HBO therapy*

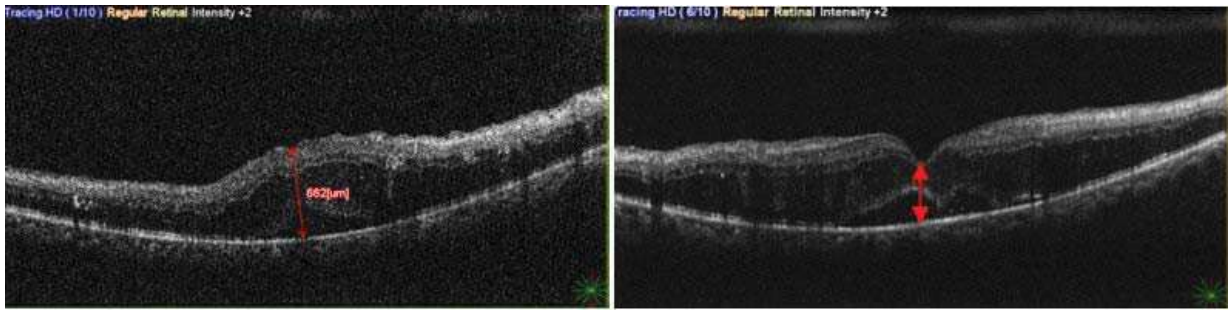

Figure 6: *Right eye after HBO therapy OCT: 662um Left eye after HBO therapy OCT: 501um.*

or reversible changes in its metabolism. This myopic shift is generally reversed within 6 weeks to 6 months after completion of therapy but it may be permanent in rare instances.[11]

Cataract formation was reported in patients underwent prolonged HBO therapy (more than 100 sessions). It is important to provide close monitoring in patients at risk for cataract formation although such prolonged therapy has been abandoned currently. Oxygen toxicity directed to lens and reactive oxygen species formed induce nuclear cataract and myopia [12]

Retrolental fibroplasia is one of the most important ocular adverse effect of oxygen toxicity, which occurs in premature newborns given supplemental oxygen therapy. Vasoconstriction occurs in the retina with immature vascularization; followed by disorganization of vascular endothelial cells and diffuse proliferation. Vascular proliferation in retina and fibrosis may result in permanent blindness.[13]

In addition, it has been suggested that oxidative stress caused by HBO therapy may worsen age-related macular degeneration, keratoconus, cataract and retinopathy. In the study, it was emphasized that negative effects of HBO therapy is caused by oxygen radicals generated by elevated oxygen concentration.[12] Yonekawa et al. reported a case with exacerbation of macular edema following HBO therapy. [14]

Recently, Tran et al. published a case report with many similar features with our case. In that case report, a 43-years old patient underwent HBO therapy for diabetic foot but pre-retinal hemorrhage was developed during follow-up and both eyes evolved to proliferative phase. As similar to our case, the patient was on insulin therapy and progression in retinopathy was documented by monitoring patient before, during and after HBO therapy. However, the case report included only one patient with HbA1c level of 7.9. Authors recommended pan-retinal photocoagulation and intravitreal anti-VGEF injection to the patient. It was emphasized that stable retinopathy was worsened in this patient[15]

In 1994, McCartney published a case reporting intravitreal hemorrhage developed on session 8 of HBO therapy given for diabetic foot in a 37-years male patient. The patient had type 1 diabetes mellitus and bilateral proliferative retinopathy, who had been receiving insulin therapy over 17 years.

In the case report, intravitreal hemorrhage was attributed to weaker physiological vasoconstriction occurring in response to increased oxygen saturation in HBO therapy in diabetic patient and response of fragile vessels in retinal neovascularization.[16] The case report also included one patient with diabetic foot. Since case series or trials are lacking in the literature, it is impossible to suggest a direct relationship between worsening in diabetic retinopathy and HBO therapy. However, we think that HBO adverse effect observed in diabetic retinopathy has similarities with prematurity retinopathy. In both instances, there is retinal tissue with impaired or abnormal vascularization and increased VGEF levels. We thinkthat such retina responds with proliferation in abnormal vessels in case of transition from elevated oxygen saturation to normal oxygen saturation.

On contrary, in a study by Chang et al., it was shown that HBO therapy reduced leakage from retinal veins in rats with diabetic retinopathy. In that study, HBO therapy was given to rats with streptozotocin-induced diabetes mellitus. When compared to controls, it was suggested that HBO therapy reduced leakage from retinal veins of diabetic rats by preserving retina-blood barrier.[17]

In our case, soft and hard exudates disappeared but flame-like retinal hemorrhages developed and one arterial embolus occurred after HBO therapy. We think that underlying reason for disappearance of soft and hard exudates is vasoconstriction response to elevated oxygen levels. We detected increased macular edema in both eyes and progression to proliferative phase in left eye despite decrease in hard exudates. This may due to poor glucose regulation and natural course of disease as no intravitreal injection was performed or HBO suggested by worsening occurred 10 days after completion of HBO. We think that diabetic retina with already elevated VGEF levels which was subjected to high levels of oxygen could respond to sudden decrease in oxygen level in this way and progressed to proliferative phase. In our case, we aimed to emphasize that close monitoring is essential during and after HBO therapy in patients with diabetic retinopathy.

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