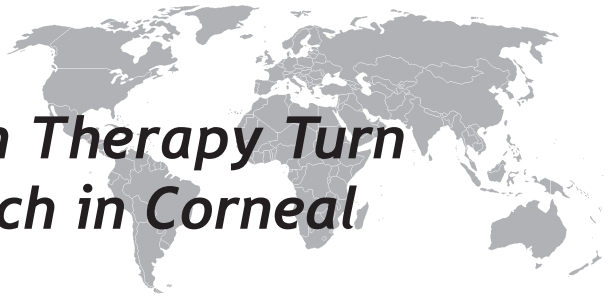

Can Hyperbaric Oxygen Therapy Turn off the Angiogenic Switch in Corneal Neovascularization?

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To the Editor;

Cornea normally does not have blood vessels. Corneal neovascularization may develop secondary to various inflammatory and infectious disorders. In corneal neovascularization, new blood vessels grow from the limbal vascular plexus into the cornea. Corneal neovascularization reduces visual acuity by disturbing corneal transparency and increases the risk of corneal graft rejection. Corneal avascularity is maintained by the equilibrium between the angiogenic and anti-angiogenic factors. A shift towards angiogenic factors in this equilibrium is called as "angiogenic switch" (1). The role of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), in the pathogenesis of corneal neovascularization has been well defined (2).

Hyperbaric oxygen therapy (HBOT), which involves the inhalation of 100% oxygen at higher atmospheric pressures, increases the amount of oxygen dissolved in the blood and that delivered to the tissues. Besides relieving tissue hypoxia, HBOT exerts various biochemical and physiological effects at cellular level (3,4). We think that HBOT may be beneficial to suppress corneal neovascularization by controlling the inflammation and release of angiogenic factors.

The main source of the VEGF in corneal neovascularization is inflammatory cells that invade the cornea (5). Therefore, inhibition of neutrophil adherence to the endothelium has been targeted in recent studies to prevent corneal neovascularization. It is showed that mice deficient for adhesion molecules on neutrophils (CD18) or endothelial cells (intercellular adhesion molecule-1; ICAM-I) developed significantly less corneal neovascularization than controls (6). The corneal neutrophil counts and VEGF mRNA levels were similarly reduced in CD18- and ICAM-1-deficient mouse compared to controls (6). HBOT decreases CD18 function on neutrophils (7) as well as the expression of ICAM-1 on endothelial cells (8). HBOT also decreases inflammation and VEGF levels by down regulation of VEGF/KDR signal axis and facilitates wound healing rate in ischemic wounds (9). Ersanli et al. demonstrated that

HBOT is as effective as corticosterods with respect to anti-inflammatory effectiveness in an experimental uveitis model (10).

Another target for HBOT may be matrix matalloproteinases (MMPs). This group of protelytic enzymes are involved in angiogenesis and in extracellular matrix remodeling. Corneal infiltrating neutrophils express matrix metalloproteinase-9 (MMP-9) and treatment with specific monoclonal antibody against MMP-9 reduces the extent of angiogenesis (11). HBOT reduces neuroinflammation and MMP-9 expression in a rat model of traumatic brain injury (12).

Taken together, we hypothesize that HBOT may control corneal neovascularization by relieving corneal hypoxia, attenuating neutrophil infiltration, and reducing VEGF and MMP-9 levels.

REFERENCES

1. *Culton M, Chandler DB, Proia AD, Hickingbotham D, Klintworth GK. The effect of oxygen on corneal neovascularization. Invest Ophthalmol Vis Sci 1990;31:1277-81.*
2. *Edelman JL, Castro MR, Wen Y. Correlation of VEGF expression by leukocytes with the growth and regression of blood vessels in the rat cornea. Invest Ophthalmol Vis Sci. 1999;40(6):1112-23.*
3. *Zheng M, Deshpande S, Lee S, Ferrara N, Rouse BT. Contribution of vascular endothelial growth factor in the neovascularization process during the pathogenesis of herpetic stromal keratitis. J Virol 2001;75(20):9828-35.*
4. *Etlik O, Tomur A. The oxidant effects of hyperbaric oxygenation and air pollution in erythrocyte membranes (hyperbaric oxygenation in air pollution). Eur J Gen Med 2006;3(1):21-8.*
5. *Aydınöz S, Süleymanoğlu S, Haholu A, Uzun G, Karademir F, Yıldız S, Göçmen I. Hyperbaric Oxygen Therapy In Calcium Chloride Extravasation Injuries: An Experimental Animal Studys. Eur J Gen Med 2007:4(4):186-9.*
6. *Moromizato Y, Stechschulte S, Miyamoto K, et al. CD18 and ICAM-1-dependent corneal neovascularization and inflammation after limbal injury. Am J Pathol 2000;157(4):1277-81.*
7. *Thom SR, Mendiguren I, Hardy K, et al. Inhibition of human neutrophil [beta]2-integrin-dependent adherence by hyperbaric O2. Am J Physiol 1997; 272: C770-C7.*
8. *Buras JA, Stahl GL, Svoboda KK, Reenstra WR. Hyperbaric oxygen downregulates ICAM-1 expression induced by hypoxia and hyperglycemia: the role of NOS. Am. J. Physiol. Cell Physiol 2000; 278: C292-C302.*
9. *Zhang Q, Chang Q, Cox RA, Gong X, Gould LJ. Hyperbaric oxygen attenuates apoptosis and decreases inflammation in an ischemic wound model. J Invest Dermatol 2008;128(8):2102-12.*
10. *Erşanli D, Karadayi K, Toyran S, et al. The efficacy of hyperbaric oxygen for the treatment of experimental uveitis induced in rabbits. Ocul Immunol Inflamm. 2005;13(5):383-8.*
11. *Lee S, Zheng M, Kim B, Rouse BT. Role of matrix metalloproteinase-9 in angiogenesis caused by ocular infection with herpes simplex virus. J Clin Invest. 2002;110(8):1105-11.*
12. *Vlodavsky E, Palzur E, Soustiel JF. Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. Neuropathol Appl Neurobiol. 2006;32(1):40-50.*