Oxygen – Nature's Miracle Drug

Shalini Grover,¹ Pradeep Shukla,¹ Deepak Grover,¹ and Neeraj Taneja²

¹Department of periodontology, D.J College of dental sciences & research, Modinagar, Distt Ghaziabad, Uttar Pradesh, India

²Department of Oral Medicine & Radiology, Subahrti Dental College & Hospital, Meerut, Uttar Pradesh, India

Correspondence to :

Shalini Grover

E-mail : drntaneja@rediffmail.com

Abstract

Oxygen is one of the most versatile and powerful agents available to the modern medical practitioner. The therapeutic use of oxygen under pressure is known as Hyperbaric Oxygen Therapy (HBO) and has been used to assist wound healing for almost 40 years. HBO has several specific biological actions like hyper-oxygenation of tissue, vasoconstriction, down regulation of inflammatory cytokines, up-regulation of growth factors, antibacterial effects, potentiation of antibiotics and leukocyte effects. Periodontitis is an inflammatory disease caused by bacterial biofilms that accumulate on the teeth. The inflammation is characterized first by an acute response that, in some cases, becomes chronic leading to destruction of bone and connective tissue attachment that is associated with a complex acquired immune response to periodontal pathogens. Several studies have described the beneficial role of HBO in the treatment of various human pathologies either alone or in combination with other therapies. Very scarce data is available to analyze the effects of HBO therapy on periodontal disease. This article looks understanding the biological and physiological effects of using O₂ underpressure and its benefit against periodontal diseases.

Keywords :

hyperbaric oxygen, periodontitis, microbiology, healing, growth factors, polymorphonuclear leucocytes

Introduction

The Committee on Hyperbaric Medicine defines Hyperbaric Oxygen Therapy as “A mode of medical treatment in which the patient is entirely enclosed in a pressure chamber and breathes 100% Oxygen at a pressure greater than 1 atmosphere absolute (ATA)”. ATA is the unit of Pressure and 1 ATA is equal to 760 mm of mercury or pressure at sea level.

HBO was first used to recompress divers by Behnke in the 1930s (1), and was developed to complement the effects of radiation in cancer treatment by Churchill-Davidson in the 1950s (2). Within a few years HBO was being used to support patients undergoing cardiac surgery, and to treat clostridial gas gangrene and carbon monoxide poisoning. HBO was first used to assist wound healing when it was noted in 1965 that burns of the victims of a coal mine explosion, treated with HBO for their CO poisoning, healed faster (3). HBO has complex effects on immunity,

oxygen transport and haemodynamics. The positive therapeutic effects come from a reduction in hypoxia and edema, enabling normal host responses to infection and ischaemia. As we learn more about how oxygen interacts with living organisms, new treatments and parameters of use are suggested. Today, the medical use of HBO, is an evolving specialty and has been successfully used in various human pathologies. Unfortunately, the data available to analyze the effects of HBO therapy on periodontal disease is very limited. This article looks at a greater understanding of the biological and physiological effects of using oxygen under pressure and its benefits in the patients with periodontal diseases.

Discussion

Physiological basis for oxygen therapy

The effects of HBO are based on the gas laws, and the physiological and biochemical effects of hyperox-

ia.

Boyle's law states that at a constant temperature, the pressure and volume of a gas are inversely proportional. This is the basis for many aspects of hyperbaric therapy, including a slight increase in chamber temperature during treatment.

Dalton's law states that in a mixed gas each element exerts a pressure proportional to its fraction of the total volume (partial pressure).

Henry's law states that the amount of gas dissolved in a liquid or tissue is proportional to the partial pressure of that gas in contact with the liquid or tissue. This is the basis for increased tissue oxygen tensions with HBO treatment.

When we normally breathe air (with 21% O₂) at sea level pressure, most tissue needs of Oxygen are met from the Oxygen combined to Hb, which is 95% saturated. 100 ml blood carries 19 ml O₂ combined with Hb and 0.32 ml dissolved in plasma. At this same pressure if 100% O₂ is inspired, O₂ combined with Hb increases to a maximum of 20 ml and the dissolved plasma level to 2.09 ml (Table 1). The high pressure applied during hyperbaric oxygen treatment pushes more oxygen into solution. The amount of O₂ dissolved in plasma increases to 4.4 ml/dl at a pressure of 2 ATA and to 6.8 ml/dl at 3 ATA. This additional O₂ in solution is almost sufficient to meet tissue needs without contribution from O₂ bound to hemoglobin and is responsible for most of the beneficial effects of this therapy (4, 5, 6).

Effects of HBO on tissues

HBO acts in numerous ways that affect tissue, they

Table 1. Effects of pressure on arterial O₂ (7)

Total pressure	Content of O ₂ dissolved in plasma (vol %)		
ATA	MmHg	Breathing air	100% O ₂
1	760	0.32	2.09
1.5	1140	0.61	3.26
2	1520	0.81	4.44
2.5	1900	1.06	5.62
3	2280	1.31	6.80

All values assume arterial pO₂=alveolar O₂ & that Hb O₂ capacity of blood is 20 vol %

are :

Vasoconstrictive effects of oxygen : Hyperoxia in normal tissues due to HBO causes rapid and significant vasoconstriction, but this is compensated for by increased plasma oxygen carriage, and microvascular blood flow in ischaemic tissue.

Oxygen diffusion effects : The beneficial effects of oxygen are primarily related to the concentration of oxygen molecules in the tissue, rather than by diffusion kinetics. However, the rate of oxygen entry into the wound environment is affected by the rate of diffusion from the capillaries. Oedema adversely affects the achievement of high oxygen concentrations in the wound and increases the intercapillary diffusion distance. Even a small increase in tissue oedema can dramatically slow the rate of entry of oxygen into the tissues and can cause tissue hypoxia.

Hyperoxygenation of tissue : The oxygenation of hypoxic tissue is one of the key mechanisms by which HBO accelerates wound healing. Numerous studies have shown a dose response curve for the provision of oxygen in the wound healing environment (8). Chronic wounds are frequently hypoxic and the provision of HBO corrects the hypoxia, albeit temporarily. It then allows for acceleration of the wound healing process by inducing neovascularisation through processes which continue long after the HBO session has ended and tissue oxygen levels have returned to pre-treatment values. Marx in 1988 demonstrated that for irradiated chronic wounds, HBO₂ induces neovascularisation, which becomes significant after about 14 treatments and continues for years after the HBO₂ therapy has ceased. A typical chronic wound will usually require 20 to 30 HBO₂ treatments. This probably represents the amount of neovascularisation needed to sustain wound healing (Fig. 1).

Cytokine down regulation and growth factor up-regulation : HBO is capable of favorably influencing a number of cytokines and growth factors important to enhance wound healing. HBO up-regulates collagen synthesis through pro- α 1(I) mRNA expression. It has also been shown to up-regulate mRNA for the platelet-derived growth factor (PDGF)-beta receptor

Fig.1. Vascular density of irradiated tissue treated with HBO (8). tcpO₂=transcutaneous oxygen pressure; LSICS= left second intercostal space (Courtesy : Marx RE. Hyperbaric oxygen in oral and maxillofacial surgery. Problem wounds and hyperbaric oxygen, Elsevier, New York. 1988 ; 65-123)

(9). In ischaemic flaps HBO up-regulates fibroblast growth factor (FGF) causing an increased effect over that seen with FGF alone. The interleukin-1 (IL-1), IL-6, and tumour necrosis factor (TNF)-alpha levels are diminished during HBO treatment. Vascular endothelial growth factor (VEGF) is up-regulated by hypoxia, yet the hyperoxia of HBO also up-regulates this factor. The effects of transforming growth factor (TGF)-beta1 and platelet-derived growth factor (PDGF)-beta are synergistically enhanced by HBO (10).

Leukocyte effects : During reperfusion, leukocytes adhere to ischaemic tissues, releasing proteases and free radicals, which leads to pathological vasoconstriction and tissue destruction. This free radical damage has been implicated in neuronal injury following ischaemia and exposure to drugs and poisons. Zamboni (11) demonstrated reduced leukocyte adherence and post-ischaemic vasoconstriction with HBO in ischaemic rat tissue. Thom (12) showed reduced lipid peroxidation with HBO in rats with carbon monoxide poisoning.

Antibacterial effects : HBO increases generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage DNA and inhibit bacterial metabolic functions. HBO is particularly effective against anaerobes, and facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria.

Role of HBO in infection

Oxygen is the key for phagocytosis and killing of bacteria by neutrophils or polymorphonuclear cells (PMNs). This process involves the production of oxygen radicals and superoxides and is directly influenced by the oxygen concentration in the tissue. As the oxygen tension falls below 30 mmHg the efficiency of bacteriocidal action of PMNs begins to drop off dramatically. Thus, increasing tissue concentrations of oxygen has a beneficial effect on the ability of PMNs to combat bacteria and prevent infection. HBO has six actions which have been used to combat clinical infection :

Support of infected hypoxic tissue : Soft tissue and bone infections are frequently accompanied by localized areas of tissue hypoxia caused by the inflammatory processes accompanying infection and by subsequent vascular thrombosis. As the infected tissue becomes infiltrated with inflammatory cells (PMNs and platelets) the PO₂ falls. Administration of HBO can cause PO₂ to increase five-fold in infected tissue (13).

Neutrophil activation : As tissue PO₂ rises, leukocyte killing of bacteria becomes much more efficient. Below a PO₂ of 30 mmHg, PMN killing is markedly reduced. Because areas of hypoxia accompany serious tissue infections, HBO is an effective means of raising tissue PO₂ to levels at which PMNs can function effectively. By raising tissue PO₂ to levels higher than that achieved by breathing oxygen at ambient pressure, bacterial killing by PMNs is further enhanced. Thus, by increasing tissue oxygen tension, a better than 'normal' antibacterial effect can be achieved (14).

Enhancement of macrophage activity : Macrophages, perform a key role in combating infection by scavenging bacteria and foreign material. Under hypoxic conditions macrophages are unable to scavenge effectively and produce peroxides. Hypoxia also induces macrophages to produce the inflammatory cytokines TNF-alpha, IL-1, IL-8, and intracellular adhesion molecule-1, which can adversely affect the response to infection (15).

Inhibition of bacterial growth : Anaerobic bacteria

Fig. 2. Effects of inspired O₂ concentration on antibiotics (18)

are particularly susceptible to increased concentrations of oxygen. The more sensitive the anaerobic organism is to oxygen, the lower the level of superoxide dismutase, an enzyme that allows cells to defend themselves against oxygen free radicals. With HBO large amounts of oxygen free radicals can be generated, making anaerobic bacteria particularly susceptible to oxidative killing (16).

Inhibition of endotoxin release: HBO appears to work by antagonising some of the harmful effects of bacterial endotoxin release. However, to be optimally effective, HBO must be given early in the course of infection and combined with appropriate surgical debridement and antibiotics (17).

Potentiation of antibiotics: Knighton et al (18) have demonstrated that Oxygen adds to the effectiveness of antibiotics; the greater the concentration of oxygen, the more pronounced the effect. This is because; HBO improves the oxygen-dependent transport of certain antibiotics across bacterial cell walls (Fig. 2).

HBO therapy and periodontal diseases

The medical and surgical conditions as accepted by the Hyperbaric Oxygen Committee of Undersea Medical Society for HBO therapy are air or gas embolism, carbon monoxide/cyanide poisoning, crush injury, compartment syndrome and other acute traumatic ischemias, decompression sickness, enhancement of healing of selected problem wounds, excep-

tional blood loss, gas gangrene, necrotizing soft tissue infections, selected refractory anaerobic infections: actinomycosis, Skin grafts or flaps (compromised), Osteomyelitis (refractory), Radiation necrosis (osteoradionecrosis) and soft tissue radiation necrosis.

Periodontitis is an inflammatory disease caused by bacterial biofilms which adhere on the teeth. The inflammation is characterized first by an acute response that, in some cases, becomes chronic leading to destruction of bone and connective tissue attachment that is associated with a complex acquired immune response to periodontal pathogens. The inflammatory and immune responses in periodontitis are a continuum of the normal host response to infection that eventually becomes the pathology when homeostasis is lost. Though there is an ample of data to support the beneficial effects of HBO therapy for various medical conditions, very few studies have been documented for its use in periodontal diseases.

Shannon M.D. et al in 1988 (19) tested oxygen effects on healing gingival wedge excisions using Sprague-Dawley rats. 40 operated controls were maintained at normal pressure in room air. 3 experimental groups of 40 rats each were exposed for 90 min daily to one of the following: [1] 20.8% oxygen at 2.4 atmospheres pressure, [2] 100% oxygen at 1 atmosphere, or [3] 100% oxygen at 2.4 atmospheres. Histometric analysis was performed using light microscopy. The controls failed to show healing comparable to experimental animals until the end of 2 weeks. Enhanced connective tissue healing was most significant in the 2.4 atmospheres pressure groups at 3 and 6 weeks when compared to controls. However, by 12 weeks, no significant differences could be detected. Early connective tissue adaptation does not imply eventual attachment as epithelial down growth progressively displaced the connective tissue adjacent to the root in both experimental and control groups.

Chen T et al in 2002 (20) reported the effects of Hyperbaric Oxygen in a controlled study of periodontitis in 24 patients. The study teeth were

divided into 4 groups based on treatment: 1-HBO therapy, 2-HBO+scaling, 3-scaling, 4-control. Highly significant differences in Gingival Indices (GI), Sulcus Bleeding Indices (SBI), Probing Depth (PD), Attachment Loss (AL), Plaque Index (PLI), and Gingival Blood Flow (GBF) were seen in the HBO, the HBO+Scaling and the Scaling Groups compared to the Control Group. The number of subgingival anaerobes as well as the number of Rods, Fusi, and Spiro were reduced markedly in these three treatment groups. Statistically greater differences in clinical indices, GBF, subgingival anaerobe number and number of Rods, Fusi and Spiro were found by comparison of HBO+Scaling and HBO Groups, as well as between the HBO+Scaling and Scaling Groups, but no significant differences were observed in GI, SBI, PD, or AL between the HBO and Scaling Groups. HBO therapy combined with scaling and root planing was the most beneficial in the treatment of periodontitis and treatment effect could last more than 1 year.

Paul Coulthard et al in 2002 (21) investigated the effectiveness of hyperbaric oxygen therapy for irradiated patients who require dental implants using data from randomized controlled clinical trials (RCTs). There were no RCTs comparing with and without HBO for implant treatment in irradiated patients.

Chen T.L. in 2003 (22) studied the therapeutic effects and holding time of hyperbaric oxygen on human severe periodontitis. 30 cases with periodontitis were selected and randomly divided into 2 groups, i.e. the HBO group were exposed to a pressure of 0.25 MPa and control group were rinsed with gargle. Gingival indices (GI), sulcus bleeding indices (SBI), plaque index (PLI), probing depth (PD), attachment loss (AL) and gingival crevicular fluid (GCF) were measured during the first and last clinical visits, and 1 year after HBO therapy. The gingival blood flow (GBF) were measured by Laser Doppler Flowmeter. HBO can decrease GI of patients with periodontitis by 1.1, SBI by 1.2, PD and AL by 0.7 mm, volume of GCF by 2.0, and significant differences could be seen in the above indices between pre

and post HBO therapy. The GBF had a 1.8 folds increase after HBO exposure. GI and SBI one year after HBO therapy were larger than that of the time after HBO therapy. There were no significant differences in the PLI, PD, AL, GCF, GBF between post HBO therapy and 1 year after HBO therapy. Thus it is concluded that HBO had good therapeutic effects on severe periodontitis and the effects lasted for more than 1 year.

Guo Y.H. et al in 2004 (23) observed the clinical effects of hyperbaric oxygen therapy combined with supragingival and subgingival scaling therapy on periodontitis. The patients with periodontitis were divided randomly into 3 groups, the supragingival and subgingival scaling therapy group, the hyperbaric oxygen therapy group, the hyperbaric oxygen combined with supragingival and subgingival scaling therapy group. The clinical index and the level of aspartate aminotransferase in gingival cervical fluid (GCF-AST) of the 3 groups were compared pre and post treatment, and the clinical index and the level of GCF-AST of the 3 groups after treatment were compared. The 3 methods had different clinical effects on periodontitis, and the hyperbaric oxygen combined with supragingival and subgingival scaling group had the best therapeutic results. The hyperbaric oxygen therapy combined with supragingival and subgingival scaling therapy had synergistic action on periodontitis.

Alexander J. et al 2006 (24) examined the effect of adjunctive local oxygen therapy in the treatment of necrotizing periodontal disease. Thirty patients with acute necrotizing periodontal disease were treated with the systemic antibiotics amoxicillin, clavulanic acid, and metronidazole. In 15 out of 30 patients, an adjunctive local oxygen therapy was administered and the patients were followed from the first to 10th day of treatment with clinical and bacteriological examinations. The clinical examination registered gingival bleeding, periodontal probing depth, and attachment loss; microbiology registered five representative bacteria by a semi quantitative DNA polymerase chain reaction test. In both groups of patients, colonization with *Prevotella intermedia*,

Tannerella forsythensis, and *Treponema denticola* was initially positive. None of these three microorganisms were completely eradicated in any of the patients in the group without oxygen therapy within the first 10 days of treatment. In the group with adjunctive oxygen therapy, all patients either showed a reduction or complete eradication of the microorganisms, resulting in more rapid clinical restitution with less periodontal destruction. Adjunctive oxygen therapy results in early eradication of pathogenic anaerobic microorganisms in cases of acute necrotizing periodontal disease and thus the damage to periodontal tissue is minimized.

Caterina S. et al in 2007 (25) evaluated the effects of HBO on a selected number of patients suffering from adult chronic periodontitis in comparison with surgical intervention (scaling and root planning, SRP), as well as the effects of a combination of both therapies on the evolution over time of the microflora of the periodontal pockets. Bacteria were detected either by culture or by a molecular method (PCR). Microbiological data indicate that the combination of HBO and SRP substantially reduced (by up to 99.9%) the gram-negative anaerobe loads of the subgingival microflora. The low values of pathogens persisted for at least two months after the therapy. HBO or SRP alone produced a temporarily more limited effect on periodontal anaerobes. Additional experimental confirmation of these results was provided by molecular detection of the main periodontopathogenic bacteria with a significant reduction in the number of dental sites which harboured them. It was also shown that HBO both alone and in combination with SRP reduced the Gingival Index value to zero and gingival health persisted for 3 months at least. Thus, in parallel with the loss of periodontopathogenic bacteria, a substantial improvement in oral health was observed. In conclusion, this study has shown that HBO may represent a useful aid, especially in combination with SRP, as far as non-surgical periodontal therapy is concerned.

Marco E et al 2008 (26) compared the success, morbidity, patient satisfaction and cost effectiveness of dental implant treatment carried out with and

without HBO in irradiated patients. Randomized controlled trials (RCT) of HBO therapy for irradiated patients requiring dental implants were selected. Thirteen patients received HBO therapy while other 13 did not. Two to six implants were placed in fully edentulous mandibles to be rehabilitated with bar-retained overdentures. One year after implant loading four patients died from each group. One patient, treated with HBO, developed an osteoradionecrosis and lost all implants so the prosthesis could not be provided. Five patients in the HBO group had at least one implant failure versus two in the control group. There were no statistically significant differences for prosthesis and implant failures, postoperative complications and patient satisfaction between the two groups.

Despite the limited amount of clinical research available, it appears that HBO therapy in irradiated patients requiring dental implants may not offer any appreciable clinical benefits. There is a definite need for more RCTs to ascertain the effectiveness of HBO in irradiated patients requiring dental implants.

Methods of Administration

Hyperbaric Oxygen may be administered in a Monoplace chamber wherein a single patient is placed in a chamber which is then pressurized with 100% Oxygen. Monoplace chambers are used to treat stable patients with chronic medical conditions. Multiplace chamber are used to treat many patients at the same time and when treating critically ill patients who require a medical attendant within the chamber. These chambers are pressurized with compressed air while the patient breathes 100% Oxygen through special masks or Oxygen Hoods. The treatment control panel controls the therapy and monitors the patient during the treatment. Most therapy is given at 2 or 3 ATA and the average duration of therapy is 60 to 90 minutes. Number of therapies may vary from 3-5 for acute conditions and from 50-60 for radiation illnesses.

Complications and Contraindications

HBO is a relatively safe treatment, but does carry

some risks, due to the increased pressure and hyperoxia. The commonest effect of oxygen toxicity is a progressive, reversible myopia, thought to be due to physical lens deformation. CNS toxicity may be due to the seizure-potentiating effect of HBO.

Middle ear and sinus barotraumas are preventable by equalization techniques or tympanostomy tubes, and otitis media can be prevented with pseudoephedrine. Inner ear barotrauma is extremely rare, but tympanic rupture can result in permanent hearing loss, tinnitus and vertigo. Pulmonary barotrauma and pneumothorax are extremely rare, particularly without pre-existing lung disease. Dental barotrauma may rarely cause pain under a dental filling.

There have been some concerns that HBO could stimulate malignant growth by increasing tumour oxygenation.

Clinical and experimental evidence does not support claims that HBO during pregnancy can cause a range of foetal complications, including spina bifida and limb defects. Psychological side-effects such as claustrophobia are common.

The only absolute contraindication to HBO is an untreated tension pneumothorax, and this must be excluded before treatment. Relative contraindications include impaired pressure equalization, and cardiac disease.

Conclusion

Hyperbaric Medicine is poised at an exciting era of revival. Hyperbaric oxygen is a powerful treatment for acting on healing tissue in a number of ways. As we learn more about how HBO benefits wounds by up-regulating growth factors, down regulating cytokines, reducing oedema, and supporting angiogenesis and new tissue ingrowths, the potential benefits to wound healing become clearer.

Evaluation of the effectiveness of oral health interventions is essential for several reasons, the most important of which is the health benefit and well-being of patients. Though the studies have concluded that HBO therapy has positive results in reducing the pathogenic microflora and improving the clinical condition in chronic periodontitis, necrotizing per-

iodontitis and in implant cases, there is a need for randomized control trials to determine the effectiveness of HBO. If these preliminary results are confirmed in further, more sizeable clinical and microbiological experiences, it may be possible to suggest an innovative, non-invasive protocol for periodontal disease therapy.

References

1. Phillips JL: Air as medicine In: Phillips JL, editor. The Bends. New Haven: Yale University Press, p197-203, 1998.
2. Churchill-Davidson I, Sanger C, Thomlinson RH: High pressure oxygen and radiotherapy. *Lancet*, 1: 1091-1095, 1955.
3. Wada J, Ikeda T, Kamata K, Ebuoka M: Oxygen hyperbaric treatment for carbon monoxide poisoning and severe burn in coal mine (Hokutanyubari) gas explosion. *Igakunoaymi (Japan)*, p54-68, 1965.
4. Leach RM, Rees PJ, Wilmshurst P: Hyperbaric oxygen therapy. *Br Med J*, 317: 1140-1143, 1998.
5. Tibbles PM, Edelsberg JS: Hyperbaric Oxygen Therapy. *NEJM*, p1642-1648, 1996.
6. Bassett BE, Bennett PB: Introduction to the physical and physiological basis of hyperbaric therapy. *Undersea Hyperb Med*, p11-24, 1986.
7. Sheffield PJ: Measuring tissue oxygen tension: a review. *Undersea Hyperb Med*, 25: 179-188, 1998.
8. Marx RE: Hyperbaric oxygen in oral and maxillofacial surgery. *Problem wounds and hyperbaric oxygen*, Elsevier, New York, p65-123, 1988.
9. Bonomo SR, Davidson JD, Yu Y, Xia Y, Lin X, Mustoe TA: Hyperbaric oxygen as a signal transducer: upregulation of platelet derived growth factor-beta receptor in the presence of HBO₂ and PDGF. *Undersea Hyperb Med*, 25(4): 211-216, 1998.
10. Wu L, Pierce GF, Ladin DA, Zhao LL, Rogers D, Mustoe TA: Effects of oxygen on wound responses to growth factors: Kaposi's FGF, but not basic FGF stimulates repair in ischemic wounds. *Growth Factors*, 12(1): 29-35, 1995.
11. Zamboni WA, Roth AC, Russell RC, Graham B, Suchy H, Kucan JO: Morphological analysis of the microcirculation during reperfusion of ischaemic skeletal muscle and the effect of hyperbaric oxygen. *Plastic Reconstr Surg*, 91: 1110-1123, 1993.
12. Thom SR: Antagonism of carbon monoxide-mediated brain lipid peroxidation by hyperbaric oxygen. *Toxicol Appl Pharmacol*, 105: 340-344, 1990.
13. Silver IA: Tissue PO₂ changes in acute inflammation. *Adv Exp Med Biol*, 94: 769-774, 1978.
14. Mader JT, Adams KR, Sutton TE: Infectious dis-

- eases : Pathophysiology and mechanisms of hyperbaric oxygen. *J Hyperbar Med*, 2 : 133-140, 1987.
15. Scannell G : Leukocyte responses to hypoxic/ischemic conditions. *New Horiz*, 4(2) : 179-183, 1996.
 16. Tally FP, Goldin BR, Jacobus NV, Gorbach SL : Superoxide dismutase in anaerobic bacteria of clinical significance. *Infect Immun*, 16(1) : 20-25, 1977.
 17. Thom SR : Hyperbaric oxygen therapy in septicemia. *J Hyperb Med*, 2 : 141-146, 1987.
 18. Knighton DR, Halliday B, Hunt TK : Oxygen as an antibiotic : the effect of inspired oxygen on infection. *Arch Surg*, 119 : 199-204, 1984.
 19. Shannon MD, Hallmon WW, Mills MP, Lane JJ, Newell DH : Periodontal wound healing responses to varying oxygen concentrations and atmospheric pressures. *J Clin Periodontol*, 15(4) : 222-226, 1988.
 20. Chen T, Zhou Y, Liu J, Xu B, Wu Z, Li D : Biological effects of hyperbaric oxygen on human severe periodontitis. *Undersea Hyperb Med*, 29(3) : 159-166, 2002.
 21. Coulthard P, Esposito M, Worthington HV, Jokstad A : Therapeutic use of hyperbaric oxygen for irradiated dental implant patients : a systematic Review. *J Dent Educ*, 67(1) : 2002.
 22. Chen TL, Lin SL, Liu GQ, Liu JC, Song PZ, Xu B, Zhang XH, Wang G, Chen J : Effects and holding time of hyperbaric oxygen on human severe periodontitis. *Shanghai Kou Qiang Yi Xue*, 12(6) : 403-405, 2003.
 23. Guo YH, Zhu BL : The clinical effects of hyperbaric oxygen therapy combined with supragingival and sublingual scaling therapy on periodontitis. *Shanghai Kou Qiang Yi Xue*, 13(4) : 333-335, 2004.
 24. Gaggli AJ, Rainer H, Grund E, Chiari FM : Local Oxygen Therapy for Treating Acute Necrotizing Periodontal Disease in Smokers. *J Periodontol*, 77(1) : 31-38, 2006.
 25. Signoretto C, Bianchi F, Burlacchini G, Canepari P : Microbiological evaluation of the effects of hyperbaric oxygen on periodontal disease. *New Microbiologica*, 30 : 431-437, 2007.
 26. Esposito M, Grusovin MG, Kwan S, Worthington HV, Coulthard P : Interventions for replacing missing teeth : hyperbaric oxygen therapy for irradiated patients who require dental implants. *Cochrane Database Syst Rev*, (3) : CD003607, 2008.