ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 4, Issue – 1, February - 2021, Page No. : 08 - 18

Hyperbaric Oxygen Therapy: Mechanism of Action and Its Application in Periodontics- A Review

[1]Dr. Harshita Gupta, Assistant Professor, Department of Dentistry, Noida international institute of medical sciences, Greater Noida, Uttar Pradesh, India.

[2]Dr. Rajkumar Kelvin, Department of Periodontology, School of Dental Sciences, Sharda University, Greater Noida, Uttar Pradesh, India.

Corresponding Author: Dr. Harshita Gupta, Assistant Professor, Department of Dentistry, Noida international institute of medical sciences, Greater Noida, Uttar Pradesh, India.

Citation of this Article: Dr. Harshita Gupta, Dr. Rajkumar Kelvin,"Hyperbaric Oxygen Therapy: Mechanism of Action and Its Application in Periodontics- A Review", IJDSIR- February - 2021, Vol. – 4, Issue - 1, P. No. 08 – 18.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Periodontal diseases are caused primarily by pathogenic bacteria. The presence of putative periodontal pathogens in the gingival crevice is not sufficient to initiate the inflammation process. Elevation of the relative proportions of these bacteria plays a crucial role in causing tissue and bone damage.[1]

Nowdays, various novel therapeutic approaches are tried as an alternative to conventional therapy or in combination with conventional therapy to reduce load of periodontopathic pathogens. One of the effective therapeutic measures can be use of hyperbaric oxygen, n (HBO_2).[2]

Although the application of compressed gas in medicine had its origins centuries ago. The use of hyperbaric therapy dates back nearly 350 years. The first hyperbaric chamber was created in 1662; Today studies continue to improve and find more uses for hyperbaric oxygen therapy.[3]

Hyperbaric literally translates to increased (hyper) pressure (baric). At sea level a person is being exposed normal atmospheric pressure or 1 ATM and breathes approximately 21% oxygen. In a hyperbaric chamber this is increased to 100% oxygen and 1.5 to 3x normal atmospheric pressure. This allows the blood to carry more oxygen and deliver 15-25 times more oxygen to the tissues and organs of the body. Oxygen has natural healing properties, and increasing the amount that is circulating throughout the body promotes faster and more efficient healing for a wide variety of diseases and ailments. It also provides numerous health benefits.[2,4.]

Mechanism of Action

Therapeutic effects of HBO can be attributed to its mechanical or hyperoxygenation effects[5-31]

(a) Hyper-Oxygenation: The effect of oxygen-heamoglobin reaction on transportation of CO2, known as "Haldane effect results from the fact that combination of oxygen with haemoglobin causes it to

become a stronger acid. This displaces CO2 fron the blood in two ways, first, When there is more acid, haemoglobin has less tendency to combine with CO2 to form carbheamoglobin. Much of the CO2 present in this form in blood is thus displaced and second, The increased acidity of the haemoglobin causes it to release an excess of H+ ions, and these, in turn, bind with bicarbonate ions to form carbonic acid which then dissociates into water and CO2, which is released from the blood into the alveoli.

(b) Bubble Size Reduction: High air pressure decreases the volume of gas bubbles in the blood 2-3 times that of normal air pressure. High oxygen (100%) intake saturates the blood plasma with oxygen. It is the primary mechanism at work in management of decompression sickness and arterial gas embolism.

(c) Vasoconstriction: Elevated levels of oxygen cause vasoconstriction that leads to a reduced blood flow without significantly affecting tissue oxygenation. Hyperbaric oxygen is used to control compartment pressures in crush injuries and to treat thermal burns.

(d) Fibroblast Proliferation/Collagen Synthesis: Oxygen is essential to make and properly organize collagen. Organized collagen is bundled into fibers (like strands in rope), which are interwoven and can be stretched in multiple directions without tearing (the collagen fibers are woven similar to fabric). Oxygen is required for the hydroxylation of proline and lysine in procollagen, several posttranslational steps in collagen synthesis(enzymes prolyl hydroxylase, lysyl hydroxylase and lysyl oxidase), formation of cross-linked triple-helices, cross-linking by lysyl hydroxylase. Higher oxygen concentrations increase the amount of collagen deposition and tensile strength. It has been shown that increasing oxygen enhances collagen synthesis and tensile strength in both animal and human subjects and can increase the level of collagen organization.

(e) Neovascularization / Angiogensis: The creation of new blood vessels, angiogenesis, is essential to the growth and survival of repair tissue. Oxygen levels directly affect the rate and quality of new blood vessel growth. Sufficient oxygen levels are required for correct collagen synthesis (posttranslational hydroxylation), without which the new capillary tubes assemble poorly and remain fragile. Supplemental oxygen accelerates blood vessel growth.

(f) Bactericidal/Bacteriostatic Effect: Hyperbaric oxygen therapy exerts both direct and indirect effects against bacteria. Direct bactericidal and bacteriostatic effects occur through the generation of oxygen free radicals. This free radical oxidizes proteins and membrane lipids, damages DNA, and inhibits metabolic functions essential for the growth of organisms.

Indirect effect of HBO2 in bacterial killing is through improving leukocytes function and is regarded as being more significant than the direct bactericidal and bacteriostatic effects. Neutrophils require oxygen as a substrate for microbial killing, after phagocytosis occurs. It inhibits production of alpha-toxin by C Welchii and is synergistic with aminoglycosides and quinolones. This is important in the treatment of gas gangrene and necrotizing tissue infection.

(g) Antibiotic Synergism: Hyperbaric oxygen has also been shown to potentiate the effects of certain antibiotics, especially aminoglycosides and sulfonamides.

(h) Increases Cell Metabolism And Energy Production: Oxygen is required for intracellular processes like biosynthesis, movement, and transport need energy to be functional, as well as for cell

survival. Oxygen dependent enzymes includes Adenosine triphosphate (ATP) for chemical energy and NADPH oxygenase for respiratory burst (reactive oxygen species release).Aerobic glycolysis, β-oxidation of fatty acids, and the citric acid cycle are tightly attached to the energy acquisition by oxidative phosphorylation and are therefore oxygen dependent.

(i) **Increases Rate Of Cell Proliferation And Reepithelialization:** Epithelial cells "march in" from the sides to close the wound and form a barrier between the wound and the environment – this is the foundation for forming new skin.Fibroblast proliferation and protein production have been reported to be optimal at 160 mmHg, i.e. at pO2 levels 2-fold to 3-fold higher than those found in healthy tissues, indicating that supplemental oxygen increases the rate of wound repair. Endothelial progenitor cells (EPCs) are essential in wound healing, and are triggered by hyperoxia through induction of nitric oxide (NO) with resulting enhancement in ischemic limb perfusion and wound healing.

(j) **Promotes Growth Factor Signaling:** Reactive oxygen species (ROS) are essential for the signaling processes of growth factors and processes such as leukocyte recruitment, cell motility, angiogenesis and extracellular matrix formation. ROS such as hydrogen peroxide (H2O2) increase vascular endothelial growth factor (VEGF) production in macrophages and keratinocytes. VEGF is a major long-term angiogenic stimulus at the wound site.Platelet-derived growth factor (PDGF) requires ROS in its role to regulate cell growth and division, and angiogenesis.

(k) **Increases Anti-Bacterial Activities**: Oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris. NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, also known as leukocyte oxidase, supports macrophage survival (delay of apoptosis) and enables dead cell cleansing by phagocytosis.

(l) **Acceleratesosteoblast Differentiation And Promotes Bone Formation:** Daily exposure to HBO accelerated the rate of osteoblast differentiation as determined by increased alkaline phosphatase activity and expression of type I collagen and Runx-2 mRNA during the early stages of culture. HBO also augmented bone nodule formation in hypoxic conditions. HBO had a more pronounced effect on these key markers of osteoblast differentiation than elevated oxygen or pressure alone. HBO accelerates the rate of osteoblast differentiation.

Rationale behind HBOT

According to Kessler et al[32], HBOT cannot significantly increase the amount of oxygen bound to hemoglobin molecules but can increase the amount of oxygen dissolved in the plasma.

The positive effects of HBOT stem from the benefit of increasing the tissue oxygen tension and/or pressure within the wound site and include.

1. Alteration of ischemic effect.
2. Reduction of edema.
3. Modulation of the production of nitric oxide.
4. Modification of the effect of growth factors and cytokines.
5. Promotion of cellular proliferation.
6. Acceleration of collagen deposition.
7. Stimulation of capillary budding.
8. Accelerated microbial oxidative killing.
9. Interference with bacterial proliferation.
10. Modulation of the immune system response.

11. Enhancement of oxygen radical scavengers, thereby reducing ischemia reperfusion injury[33].

Types of HBO Chambers

These include:

Multiplace chambers: These units can accommodate between 2 and 18 or more patients and commonly incorporate a minimum pressure capability of 6.0 ATA.

Advantages

1. Constant patient attendance and evaluation (particularly useful in treating evolving neurological diseases such as decompression sickness and cerebral arterial gas embolism).
2. Multiple patients treated per session.
3. Greater working pressure.

Disadvantages

1. Higher capitalization requirements.
2. Major space requirements; basement and/or ground floor level limitations.
3. Higher operating costs.

Monoplace chambers - They were designed for single occupancy and usually constructed of acrylic, having a pressure capability of 3.0 ATA, and compressed with 100% oxygen. The high flow oxygen requirement is ideally supplied via a hospital's existing liquid oxygen system.

Advantages

1. Cost efficient delivery of HBO2.
2. No risk of decompression sickness.
3. Portable, less space, less equipments, no hood or mask.
4. No risk of iatrogenic decompression sickness in patient or staff.

Disadvantages

1. Relative patient isolation.
2. Associated fire hazard.
3. Inability to use certain diagnostic and/or therapeutic equipment.

Silicon Trays

The silicon tray as delivered. Oxygen can be supplied via an anterior valve. B) The silicon tray trimmed to the right length with a pair of scissors. The tray should be adjusted to the individual patient to create a tight fit with the mucous membrane while allowing the oxygen unimpeded access to the gingiva.

The silicon tray as delivered. Oxygen can be supplied via an anterior valve. B) The silicon tray trimmed to the right length with a pair of scissors. The tray should be adjusted to the individual patient to create a tight fit with the mucous membrane while allowing the oxygen unimpeded access to the gingiva.

These trays are made up of silicon and oxygen can be supplied to these trays via an anterior valve. The silicon trays are trimmed to the right length and should be adjusted to the individual patient to create a tight fit with the mucous membrane while allowing the oxygen unimpeded access to the gingiva.

Indications

1. Air or gas embolism.
2. Carbon monoxide poisoning or carbon monoxide poisoning complicated by cyanide poisoning.
3. Clostridal myositis and myonecrosis (gas gangrene).
4. Crush injury, compartment syndrome, and other acute traumatic ischemia.
5. Decompression sickness.
6. Enhancement of healing in selected problem wounds; a. Diabetically derived illness, such as diabetic foot, diabetic retinopathy, diabetic nephropathy.
7. Exceptional blood loss (anemia).
8. Intracranial abscess.
9. Necrotizing soft tissue infections (necrotizing fasciitis).
10. Osteomyelitis (refractory).
11. Delayed radiation injury (soft tissue and bony necrosis).
12. Skin grafts and flaps (compromised).
13. Thermal burns.

CONTRAINDICATIONS

Absolute Contraindications

a) Untreated pneumothorax
b) Bleomycin
c) Cisplatin
d) Disulfiram
e) Doxorubicin
f) Sulfamylon

Relative Contraindications

a) Asthma
b) Claustrophobia
c) Congenital spherocytosis
d) Chronic obstructive pulmonary disease (COPD)
e) Eustachian tube dysfunction
f) High fever
g) Pacemakers or epidural pain pump
h) Pregnancy
i) Seizures
j) Upper respiratory infection (URI)

Effects of Hyperbaric Oxygen Therapy on Periodontal Disease

Mechanism

Hyperbaric oxygen therapy showed to increase oxygen distribution at the base of the periodontal pocket which is deleterious to periodontal pathogens, particularly to the anaerobic microorganisms. Cultivation of plaque microorganisms from sites of chronic periodontitis reveals high percentages of anaerobic (90%) bacterial species.[35] HBO2 increases generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage deoxyribonucleic acid and inhibit bacterial metabolic functions. It also facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria. HBO2 also improves the oxygen-dependent transport of certain antibiotics across bacterial cell walls. In this way HBOT results in inhibition of bacterial growth.

While on the other hand, HBOT would also allow the ischemic tissues to receive an adequate intake of oxygen sufficient for a rapid recovery of cell metabolism. Oxygen tension in periodontal pockets is very low (pO2 5-27 mmHg) when compared with atmospheric pO2 (155 mmHg), the arterial blood pO2 (95 mmHg), and the venous blood pO2 (20-40 mmHg).[37,38] Fibroblast and leukocyte function are severely compromised when pO2 is ≤30 mmHg. HBO2 increases collagen formation for capillary growth. HBO2 also promotes fibroblast

replication and collagen formation, while the patient is in the hyperbaric chamber. It also increases bactericidal function of leukocytes. HBOT also improve gingival microcirculation and increase gingival blood flow.

Thus in periodontal tissues, HBOT showed to have a deleterious effect on periodontal microorganisms as well as beneficial effects on periodontal healing by raising oxygen tension in pocket.

Evidence

Guentherman, Bishop, Collings, Dorm,[39] showed through an experiment that Periodontal pathology induced in dogs, was treated with hyperoxygenation. Blood oxygen tensions were elevated to at least 1900 mm Hg. by means of a hyperbaric oxygen chamber for two hours twice a day, two days a week for four weeks. Clinical appearance and loss of alveolar bone was recorded in treated and untreated animals. The animals receiving hyperbaric oxygen had gingival tissues that appeared clinically healthy and were found to have only modest bone loss at the end of eight weeks. On the other hand the control animals often had grossly inflamed gingiva and marked loss of bone at the end of the eight week period.

Manhold, Weisinger,Rustog [40] showed through an experiment that some commercially available oxygenating agents demonstrated shorter healing times when applied on inflamed gingiva.

Hirsch et al.[41] studied the effect of locally released oxygen on the development of plaque and gingivitis in man and concluded that there was no significant effect of oxygen on plaque formation, crevicular fluid flow, or the number of gingival bleeding sites.

Schlagenhauf et al.[42] and Annie V. Issac et al. [43] used repeated subgingival oxygen irrigations in previously untreated periodontal patients. They concluded that repeated oxygen insufflations resulted in a significant clinical improvement of the periodontal baseline conditions superior to the one found in the control.

Gaggl et al.[44] applied localized oxygenation in contrast to systemic oxygen therapy, to help treat acute necrotizing periodontal diseases. In both group of patients, colonization with Prevotella intermedia, Tannerella forsythia, and Treponema denticola was initially positive. None of these microorganisms were completely eradicated in any of the patients in the group without oxygen therapy within the first 10 days.

Signoretto et al.[45] evaluated the effects of HBO2 on 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 and found that the combination of HBO2 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 2 months after the therapy. HBO2 or SRP alone produced a temporarily more limited effect on periodontal anaerobes. In addition, molecular detection of the main periodonto-pathogenic bacteria significantly reduced in the number of dental sites, which harbored them.

Nogueira-Filho et al.[46] evaluated the effect of HBOT as an adjunct to SRP on the treatment of severe cases of periodontitis. They concluded that HBOT had a short term beneficial effect on pocket reduction and bacterial elimination, and may be considered potential adjunct therapeutic option to improve the clinical outcomes of scaling in severe cases of chronic periodontitis.

Chen et al.[47] investigated the effects of HBO2 on aggressive periodontitis (AgP), and subgingival obligate anaerobes in Chinese patients and concluded that HBO2 inhibits the growth of subgingival obligate anaerobes and facultative anaerobes and Bacteroides melaninogenicus

thus promoting healing of peridontium, which will be of help in the treatment of AgP. HBO2 therapy combined with SRP appears to be even better for synergistic treatment of AgP. The effects can last >2 years.

Ganesha et al. [48] evaluated the efficacy of HBOT as an adjunctive therapy for patients suffering chronic periodontitis, after applying the conventional therapy of scaling and root planing (SRP). Also, the study aimed to investigate the required number of HBOT sessions for treatment. Fifty four patients aged 30-50 years with chronic periodontitis and 4-6 mm of pocket depth were divided into three treatment groups: SRP treatment only, SRP with 8 sessions of HBOT, and SRP with 16 sessions of HBOT. As clinical data, pocket depth, clinical attachment level and bleeding on probing were monitored for a period of up to one month. The results showed that HBOT can be beneficial as an adjunctive therapy of chronic periodontitis when combined with SRP, and that 8 sessions of HBOT is sufficient for the purpose.

Marx et al.[49],evaluated Eighteen bony reconstructions of the mandible or maxilla using a newly defined and specific hyperbaric oxygen protocol are reported. Eleven of 12 grafts in irradiated tissue met six rigid criteria for a 91.6% rate of success. All six grafts into scarred and deficient tissue beds also met the same criteria, for an overall success rate of 94%. The rationale for emphasizing preoperative tissue preparation using hyperbaric oxygen is discussed, as are the mechanisms of action of hyperbaric oxygen on a biochemical, cellular, and tissue level. Neovascularity and neocellularity are demonstrated histologically by human biopsy specimens, and this is suggested as being the reason for the excellent results of reconstruction in irradiated and/or deficient tissue beds.

Hyperbaric Oxygen and Implant

Dental implants offer a way to replace missing teeth. Patients who have undergone radiotherapy or surgery may benefit from reconstruction with implants.

Mechanism

Hyperbaric oxygen has been shown to affect angiogenesis, bone metabolism bone turnover. In relation to radiotherapy, HBO2 can thus counteract some of the negative effects from irradiation and actually act as a stimulator of osseointegration. The exact mechanisms at the cellular level where HBO2 act remain obscure. It has been recently shown that HBO2 and basic fibroblast growth factor (bFGF) acts synergistically in irradiated bone. Factors that could be involved in bone protection by bFGF and HBO2 are bone marrow radioprotection, induction of oxygen radical scavengers and production of different cytokines.

Hyperbaric oxygen and bFGF can also enhance the level of insulin-growth factor, which is known to promote proliferation and differentiation of bone. They could also affect bone progenitor cells by promoting DNA synthesis, stimulating enzymes involved in bone formation or affect membrane receptors. HBO2 has furthermore been shown to affect the interface between the titanium implant and bone, which could be different from cellular effect.

Oxygen under hyperbaric conditions could thus play a role in osseointegration by affecting bone cell metabolism, implant interface and capillary network in the implant bed.

Evidence

Taylor and Worthington[50] reported that when implants were placed in conjunction with HBOT healing was more reliable, although still slow. They recommended HBO2 for patients treated with >50 Gy.

Johnsson[51] investigated the influence of a single 15-Gy dose of irradiation on the capacity of titanium screws to integrate in irradiated bone tissue. The biomechanical

force necessary to unscrew the titanium implants 8 weeks after placement was 54% lower for implants in irradiated bone tissue compared to implants in non-irradiated bone tissue. Post-irradiation use of hyperbaric oxygen treatment at 2.8 ATA (2-hour daily treatments for 21 days) increased the biomechanical force necessary to unscrew the titanium implants by 44% in irradiated bone and by 22% in non-irradiated bone.

Andersson[52], concluded that the Implant treatment for oral rehabilitation can be carried out as a safe and successful procedure in the irradiated patient without adjunctive hyperbaric oxygen therapy.Marx and Morales[53] reported a 5-year survival in 622 out of 748 osseointegrated implants after HBO2 treatment.

Granström et al.[54] in a case-controlled study found that about 53.7% implants failed in the irradiated group compared to 13.5% in nonirradiated group and 8.1% for irradiated HBO2treated group.he concluded that the implant insertion in irradiated bone is associated with a higher failure rate. Adjuvant HBO treatment can reduce the failures.Johnsson et al[55] concluded that irradiation reduces the capacity for osseointegration of titanium implants. Hyperbaric oxygen treatment may improve bone formation and especially has positive effects on bone maturation after irradiation.

Granstrom [56] and Teoh et al [57] concluded that the adjunctive use of hyperbaric oxygen treatment with implant installation is strongly recommended. Brandt and Balanoff [58], concluded that using an accepted hyperbaric oxygenation protocol when placing and restoring immediate implants in their case report resulted in a successful treatment outcome.

Esposito et al.[59] and Coulthard et al.[60] in a systematic review found only one randomized controlled trials (RCTs) comparing HBO2 with no HBO2 for implant treatment in irradiated patients and they concluded that HBOT 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 HBO2 in irradiated patients requiring dental implants.Grecchi et al.[61] in case of mandible osteonecrosis after a severe peri-implant infection observed risk of developing osteonecrosis of the jaw for oral implants is low after HBO therapy. Nyberg et al.[62], Chambrone et al[63], Wadhawan et al.[64] and Shah, et al.[65] concluded that the HBO can be the effective treatment protocol for the implant treatment in irradiated maxillofacial patients.

Conclusion

Hyperbaric oxygen has been successfully used in several medical applications. It has been described as “a therapy in search of diseases.”

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 few studies havebeen conducted to analyze the effects of HBO therapy on periodontal disease.

Although available evidences are few, HBOT was shown t o improve gingival blood flow and microcirculation, inhib it thegrowth of periodontal pathogens in periodontal pocke t when used alone or in combination with conventional per iodontaltherapy. In future, further research will required to be conducted to prove potential benefits of HBOT.

Reference

1. Mahale SA, Kalasva PK, Shinde SV. Hyperbaric oxygen therapy in periodontal diseases. J Int Clin Dent Res Organ 2013;5:3-8.
2. Popat RP, Popat PR. Role of hyperbaric oxygen therapy in the treatment of periodontitis. SRM J Res Dent Sci 2014;5:102-5.
3. Availablehttp://newlifemedgroup.com/history-of-hyperbaric-oxygen-therapy/

4. Jain N, Deepa D. Applications of hyperbaric oxygen t herapy in dentistry: A mini review.J Interdiscip Dentis try 2014;4:27-32.
5. Availablehttp://www.centrehyperbare.com/pdfs/hyper bare-mechanism-of-action.pdf
6. Availablehttps://www.ncbi.nlm.nih.gov/pubmed/2498 4320
7. Availablehttps://www.ncbi.nlm.nih.gov/pubmed/1801 9088
8. Ertracht O, Arieli R, Arieli Y, Ron R, Erlichman Z, Adir Y. Optimal oxygen pressure and time for reduced bubble formation in the N2-saturated decompressed prawn. J Appl Physiol 98: 1309 –1313, 2005.
9. Availablehttps://www.anesth.uiowa.edu/clinicscenters /hyperbaricmedicine/abouthbo/mechanismofaction
10. Availablehttp://www.scopemed.org/?mno=11098#abs tract
11. Availablehttp://emedicine.medscape.com/article/1464 149-overview#a2
12. Boerema I, et al. Life without blood. A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood. J Cardiovascular Surg. 1960. 1:133-146.
13. Availablehttp://www.hyperbaric.im/page_119780.htm l
14. Nylander G, Lewis D, Nordstrom H, et al. Reduction of postischemic edema with hyperbaric oxygen. Plast Reconstr Surg. 1985; 76(4):596-603.
15. Waili NS. Hyperbaric Oxygen in the Treatment of Patients With Cerebral Stroke, Brain Trauma, and Neurologic Disease. Advances in Therapy. 2005;22(6):659-78.
16. Availablehttp://www.eo2.com/resources/how-oxygen-works.pdf
17. Siddiqui A, Davidson JD, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: a new physiologic concept. Plast Reconstr Surg 1997; 99: 148–155.
18. Hohn DC, Ponce B, Burton RW, Hunt TK. Antimicrobial systems of the surgical wound. I. A comparison of oxidative metabolism and microbicidal capacity of phagocytes from wounds and from peripheral blood. Am J Surg 1977; 133: 597– 600.
19. Mirhij NJ, Roberts RJ, Myers MG. Effects of hypoxemia upon aminoglycoside serum pharmacokinetics in animals. Antimicrob Agents Chemother. 1978 Sep. 14(3):344-7.
20. Muhvich KH, Park MK, Myers RAM, Marzella L. Hyperoxia and the Antimicrobial Susceptibility of Escherichia coli and Pseudomonas aeruginosa. Antimicrobial agents and chemotherapy, 1989;33(9): 1526-30.
21. Levent et al. Ozone Therapy and Hyperbaric Oxygen Treatment in Lung Injury in Septic Rats. Int. J. Med. Sci. 2011; 8(1):48-55.
22. Smith JL. The pathological effects due to increase of oxygen tension in the air breathed. Annales de Chimie.1849:19-35.
23. Prabowo, S., et al. Hyperbaric Oxygen Treatment in a Diabetic Rat Model Is Associated with a Decrease in Blood Glucose, Regression of Organ Damage and Improvement in Wound Healing. Health,2014;6:1950-58.
24. Wadhawan R , Reddy Y , Luthra K , Gajjar D, Solanki G. Hyperbaric oxygen therapy; utility in medical & dental fields a review . Journal of Science ,2014;4(10) :604-14.
25. Gottrup F. Oxygen in wound healing and infection. World J Surg 2004;28:312–5.
26. Tandara AA, Mustoe TA. Oxygen in wound healing-more than a nutrient. World J Surg 2004;28:294–300.

27. Sheikh AY, Gibson JJ, Rollins MD, et al. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. Arch Surg 2000;135:1293–7.
28. Marx RE. Radiation injury to tissue. In: Kindwall EP, editor. Hyperbaric Medicine Practice. 2nd ed. Flagstaff (AZ): Best Publishing Company; 1999. p. 665–723.
29. Feldmeier JJ. Hyperbaric Oxygen and Wound Healing in the Head and Neck.
30. Hadia H A, Smerdonb G R, Fox S W. Hyperbaric oxygen therapy accelerates osteoblast differentiation and promotes bone formation. J dentistry2015;43:382-83.
31. Svalestad et al. Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa. Int J Oral Maxillofac Surg. 2013:1-6.
32. Kessler L, Bilbault P, Ortega F, Grasso C, Passemard R, Stephan D, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers. Diabetes Care 2003; 26: 2378–82.
33. Thackham JA, McElwain DL, Long RJ. The use of hyperbaric oxygen therapy to treat chronic wounds: A review. Wound Rep Reg. 2008;16:321–330.
34. Gupta V, Vijay S, Gupta R, Koul S. Hyperbaric Oxygen Therapy. JK-Practitioner2005;12(1):44-47.
35. Teughels W, Quirynen M, Jakubowics N. Periodontal microbiology. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, editors. Carranza's Clinical Periodontology. 11th ed. St. Louis, Missouri: Saunders Publication; 2012.
36. Signoretto C, Bianchi F, Burlacchini G, Canepari P. Microbiological evaluation of the effects of hyperbaric oxygen on periodontal disease. New microbiologica,2007;30:431-37.
37. Tanaka M, Hanioka T, Takaya K, Shizukuishi S. Association of Oxygen Tension in Human Periodontal Pockets With Gingival Inflammation. J Periodontol .1998;69:1127-30.
38. Mettraux GR, Gusberti FA, Graf H. Oxygen Tension (p02) in Untreated Human Periodontal Pockets. . J Periodontol .1984;55(9):516-21.
39. Guentherman RH, Bishop JG, Collings KC, Dorman H. The Effect of Increased Blood Oxygen Tensions on Induced Periodontal Disease. J Periodontol .1972;43(4):233-36.
40. Manhold JH, Weisinger E, Rustogi K. Gingival tissue oxygenation: The eff ect of daily application of four commercial preparations. J Periodontol 1974;45:312-3.
41. Availablehttps://www.ncbi.nlm.nih.gov/pubmed/6941974
42. Schlagenhauf U, Horlacher V, Netuschil L, Brecx M. Repeated subgingival oxygen irrigations in untreated periodontal patients. J Clin Periodontol 1994;21:48-50.
43. Annie V. Issac et al. Management of Chronic Periodontitis Using Subgingival Irrigation of Ozonized Water: A Clinical and Microbiological Study. Journal of Clinical and Diagnostic Research. 2015;9(8): ZC29-33.
44. Gaggl AJ, Rainer H, Grund E, Chiari FM. Local oxygen therapy for treating acute necrotizing periodontal disease in smokers. J Periodontol 2006;77:31-8.
45. Signoretto C, Bianchi F, Burlacchini G, Canepari P. Microbiological evaluation of the eff ects of hyperbaric oxygen on periodontal disease. New Microbiol 2007;30:431-7.
46. AvailableHttps://www.ncbi.nlm.nih.gov/pubmed/20462143

47. Chen TL, Xu B, Liu JC, Li SG, Li DY, Gong GC, et al. Eff ects of hyperbaric oxygen on aggressive periodontitis and subgingival anaerobes in Chinese patients. J Indian Soc Periodontol 2012;16:492-7.
48. Wandawa G, Mustaqimah DN, Sidik S, Saraswati H, Putri FA, Auerkari EI. Efficacy of Hyperbaric Oxygen Therapy as an Adjunctive Therapy of Chronic Periodontitis. J Int Dent Med Res 2017;10(1):72-5.
49. Availablehttps://www.ncbi.nlm.nih.gov/labs/articles/7045303/
50. Availablehttps://www.ncbi.nlm.nih.gov/pubmed/8455170
51. Johnsson K, Hansson A, Granström G, Jacobsson M, Turesson I. The Effects of Hyperbaric Oxygenation on Bone-Titanium Implant Interface Strength With and Without Preceding Irradiation. Int j oral maxillofac implants 1993;8:415-19.
52. Andersson G, Andreasson L, Bjelkengren G. Oral Implant Rehabilitation in Irradiated Patients Without Adjunctive Hyperbaric Oxygen. Int j oral maxillofac implants 1998;13:647–54.
53. Availablehttps://www.ncbi.nlm.nih.gov/pubmed/9421676
54. Availablehttp://www.joms.org/article/S0278-2391(99)90059-9/pdf
55. Johnsson et al. A Histomorphometric Study of Bone Reactions to Titanium Implants in Irradiated Bone and the Effect of Hyperbaric Oxygen Treatment. Int j oral maxillofac implants 1999;14:699–706.
56. Granstrom G. Radiotherap, osseointegration and hyperbaric oxygen therapy.Periodontol 2000,2003;33:145-162.
57. Teoh et al. Implant prosthodontic rehabilitation of the fibula-free flap reconstructed mandibles: a memorial sloan kettering cancer center review of prognostic factors and implant outcomes.Int j oral maxillofac implants2005;20:738-46.
58. Brandt RL, Balanoff W. Immediate Placement of Implants and Appliance in an Irradiated Patient:A Case Study. Clinical Implant Dentistry and Related Research,2007;9(2):116-19.
59. Availablehttp://www.cochrane.org/CD003603/ORAL_interventions-for-replacing-missing-teeth-hyperbaric-oxygen-therapy-for-irradiated-patients-who-require-dental-implants
60. Coulthard et al. Hyperbaric oxygen therapy for irradiated patients who require dental implants: a Cochrane review of randomised clinical trials. Eur J Oral Implantol 2008;1(2):105–10.
61. Grecchi F, Zollino I, Candotto V, Gallo F, Rubino G, Giglio S, et al. A case of mandible osteonecrosis after a severe periimplant infection. Dent Res J 2012;9:S233-6.
62. Nyberg et al. osseointegration of implants in irradiated with or without hyperbaric oxygen treatment: an experimental study in rat tibiae. Int j oral maxillofac implants2013;28:739-46.
63. Chambrone L, Mandia J, Shibli JA, Romito GA, Abrahao M. Dental Implants Installed in Irradiated Jaws: A Systematic Review. JDR Clinical Research Supplement 2013;92:119S-130S.
64. Wadhawan R, Reddy Y, Luthra K, Gajjar D, Solanki G. Hyperbaric oxygen therapy; utility in medical & dental fields a review. Journal of Science 2014;4(10):604-14.
65. Shah DN, Chauhan CJ, Solanki JS. Effectiveness of hyperbaric oxygen therapy in irradiated maxillofacial dental implant patients: A systematic review with meta-analysis. J Indian Prosthodont Soc 2017;17:109-19.