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Recent Advances in Hyperbaric Oxygen Therapy

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Hyperbaric Medicine is the fascinating use of barometric pressure for delivering increased oxygen dissolved in plasma to body tissues. Hyperbaric oxygen therapy (HBO) is a form of treatment in which a patient breathes 100% oxygen at higher than normal atmospheric pressure that is greater than 1 atmosphere absolute (ATA). Therapy is given in special therapeutic chambers, which were earlier used primarily to treat illnesses of deep sea divers. In the sixties HBO went out of practice because of its use without adequate scientific validation. Over the last two decades, animal studies, clinical trials and well-validated clinical experience has proved efficacy of HBO in many indications and there is recently a renewed interest in this field all over the world. Acute traumatic wounds, Crush injuries, Burns, Gas gangrene and compartment syndrome are indications where addition of Hyperbaric oxygen may be life and limb saving. Patients who have been suffering with non healing ulcers, Decubitus Ulcers (Bed sores) and all late sequelae of Radiation therapy are also benefited with HBO therapy. Acute hearing loss and many neurological illnesses are also now known to possibly benefit from Hyperbaric Oxygen Therapy. With continuing growth all over the world Hyperbaric Medicine has found a distinct role in the modern era of evidence-based medicine. This article aims to give a brief overview of the rationale, existing trends and applications of this therapy.

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.

Over the past 40 years Hyperbaric oxygen therapy (HBO) has been recommended and used in a wide variety of medical conditions, often without adequate scientific validation of efficacy or safety. Consequently a high degree of medical scepticism had developed regarding its use.[1] Gabb and Robin in the "Chest" (1987) have highlighted the controversies relating to HBO and have documented 132 past and present indications for HBO therapy.[2] Over the last two decades,
animal studies, clinical trials have produced reasonable scientific evidence or well validated clinical experience. This has now produced a set of indications for which HBO is beneficial.[3-5] In these conditions early referral is essential.[1]

This has led to a renaissance of HBO, and hyperbaric facilities now form an important part of many hospitals all over the world. China leads with 2600 Hyperbaric centers, Russia: 2000, Japan: 400, approx 200 in the UK, 400 all over Europe and approx 800 in the US. In Asia: Malaysia 5 centers, Middle East: 10, 1 in Srilanka and 1 emerging in Bangladesh. In 1999 there were 500 hyperbaric facilities in USA and presently 800 with an annual increase in the number of Hyperbaric centers and increase in patients at the rate of 15 and 620 respectively and this same rate of growth continues.[5,6] The reimbursement for HBO during the period 1995 to 1998 was to the tune of 50 million USD and recently with the approval of HBO as treatment for diabetic foot lesions, this figure is likely to double. With this continuing growth all over the world Hyperbaric Medicine has found a distinct role in the modern era of evidence based medicine.

Physiological Basis

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 that dissolved in plasma to 2.09 ml (Table 1). The higher pressure 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.[1,5,7]

Table1. Effect of Pressure on Arterial O_2

Total Pressure		Content of Oxygen Dissolved in plasma (vol %)	
ATA	MmHg	Breathing Air	100% Oxygen
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 pO_2 = alveolar O_2 and that Hb O_2 capacity of blood is 20 vol %

Method 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 to 50-60 for radiation illnesses.[8]

Toxic Effects/ Complications

When used in standard protocols hyperbaric oxygen therapy is safe. Commonest side effect may be slight pain in the ears (aural barotrauma) due to a blocked Eustachian tube. Pneumothorax and air embolism and transient reversible myopia after prolonged HBO therapy are rare complications. An occasional patient may be claustrophobic. Fire is a realistic hazard but preventable by strict safety procedures.[9,10]

Therapeutic Effects Of HBO

- **Hyperoxygenation** causes (i) Immune stimulation by restoring WBC function and enhancing their phagocytic capabilities and (ii) Neo-vascularization in hypoxic areas by augmenting fibroblastic activity and capillary growth. This is useful in radiation tissue damage and other problem wounds.
- **Vasoconstriction** reduces edema and tissue swelling while ensuring adequate Oxygen delivery and is thus useful in acute trauma wounds and burns.
- **Bactericidal** for anaerobic organisms & inhibits growth of aerobic bacteria at pressures > 1.3 ATA. It Inhibits production of alpha-toxin by C Welchii and is synergistic with Aminoglycosides and Quinolones. Thus it is life saving in gas gangrene and severe necrotising infections.
- **Reduces half-life of Carboxyhaemoglobin** from 4 to 5 hours to 20 minutes or less and is the treatment of choice for Carbon Monoxide poisoning in fire victims.
- **Mechanical effects**: Direct benefit of increased pressure helps reduces bubble size in Air Embolism and Decompression Illnesses.
- **Reactivates " sleeping cells " in the penumbra** region around central dead neuronal tissue. This is the basis of its use in neurological conditions. **It also reduces adherence of WBCs to capillary walls** and maybe useful in acute brain and spinal cord injury.

Beneficial effects of HBO

Following are some of the reasons that HBO is gaining acceptance rapidly the world over.

- Safe therapy with very few and minor side effects
- Addition of HBO obviates the need for frequent surgical procedures, promotes healing and early mobilization of the patient.
- Reduces length of hospitalization and thereby overall treatment and rehabilitation costs.
- Only treatment available in some indications.
- Emerging role in indications which have lifetime disabilities

HBO In Wounds Healing

Hyperbaric Oxygen Therapy can play a significant role when combined with conventional therapy in the following types of wounds.

A. <u>Problem Wounds</u>

(Wounds which fail to respond to established medical and surgical management for more than 30 days)

Indications of HBO

Table 2: Indications for Hyperbaric Oxygen Therapy

A. UNIVERSALLY ACCEPTED: These indications are supported with peer reviewed proof of efficacy

Wounds:
- Problem, non-healing wounds and ulcers (diabetic, venous etc)
- Infective wounds - gas gangrene, refractory osteomyelitis, necrotising soft tissue infections
- Acute traumatic ischemias, crush injuries, compartment syndromes
- Compromised skin grafts and flaps
- Thermal burns

Oncology:
- Late radiation induced tissue damage and complications due to endarteritis
- Prophylactically adjunctive to therapeutic radiation, for preparation of surgery or implant procedures in previously irradiated fields

Primary Line of Treatment:
- Air or gas embolism
- Decompression Sickness
- Carbon Monoxide poisoning, smoke inhalation

Other Indications
- Acute Sensorineural Hearing Loss
- Intracranial Absceses
- Bells Palsy

B. RESEARCH INDICATIONS: Role of HBOT in these indications is being studied in international trials
- HBOT in neurological illnesses – cerebral palsy, stroke, head injury
- HBOT as a radiosensitiser in Glioblastoma mutiforme and re-irradiation of sqamous cell Ca

Diabetic wounds: Despite best efforts many diabetic patients develop skin ulcers especially on the feet. Other wounds such as sternal (post CABG) wounds and grafts also have great difficulty in healing in diabetics. Wound care strategies, which include hyperbaric therapy, have been proved to be cost effective with reduced amputations thereby vastly improving the quality of life for these patients.[11,12]

Vascular insufficiency ulcers: HBO is recommended in selected wounds, which do not heal despite maximum revascularization. Additionally for preparation of a granulating bed for skin grafting in areas with poor circulation such as venous ulcers.[13-15]

The Wagner Classification System for Dysvascular Foot Lesions is used to evaluate patients with problem wounds. Patients with Class 3, 4, or 5 Wagner lesions are recommended HBO.[16-17]

B. Infective Wounds

Clostridial Myositis & Myonecrosis (Gas Gangrene): Clostridium bacteria are "anaerobic," and their replication, migration, and exotoxin production is inhibited on exposure to high oxygen during Hyperbaric Oxygen Therapy. It is well established that addition of hyperbaric Oxygen helps in these gravely ill patients saves life and possibly limb amputation.[18]

Refractory Osteomyelitis: Osteomyelitis causes low oxygen tension in infected bones. Studies show that elevating the oxygen tensions in affected bones and the surrounding tissues helps speed healing. Hyperbaric oxygen provides adequate oxygen for fibroblast activity, augments certain antibiotics (aminoglycosides, vancomycin, quinolones and certain sulfonamides), and prevents polymorphonuclear leukocytes from adhering to damaged blood vessel linings.[19,20]

The Cierny – Mader classification of osteomyelitis can be used as a guide to determine which types of osteomyelitis may be benefited by adjunctive HBO. It should be used in patients with stage 3B or 4B osteomyelitis along with appropriate antibiotics, surgical debridement, nutritional support, and reconstructive surgery.

Necrotizing Soft Tissue Infections: Necrotizing infections like Crepitant anaerobic cellulitis, progressive bacterial gangrene, necrotizing fasciitis, and nonclostridial myonecrosis cause hypoxia in surrounding tissues, impair neutrophil activity and thus anaerobic bacteria proliferate. The infection also triggers occlusive endarteritis. It is well documented that death rates are lower among patients with necrotizing infection who receive HBO treatments plus standard therapy (debridements and antibiotics), and they require fewer debridements.[21]

C. Trauma Wounds

Crush Injury: When body tissues are severely traumatized such as in accidents, falls, and gun shot wounds, the rate of complications such as infection, non-healing of fractures, and amputations range up to 50%. As an adjunct to orthopedic surgery and antibiotics, HBO therapy can significantly decrease costs and complications**.** The Gustilo Classification is used for evaluating the use of HBO in Crush Injuries and those in Class III A, B & C (Compromised host, Flaps or grafts required to obtain soft tissue coverage and Major (macro

vascular) vessel injury) are recommended HBO treatment for better results at lower costs.[22, 23]

Acute traumatic ischemias: The Mess Score is used to evaluate the role of HBO for Mangled Extremities. Those with Mess Score 7 & 8 (Uncompromised host where age, hypotension, and mild-to-moderate ischemia significantly contribute to the score) Scores 5, 6 (Compromised hosts with diabetes, peripheral vascular disease, collagen vascular disease, etc.) and with score 3, 4 (Severely compromised hosts with advanced levels of the above conditions) are strongly recommended HBO therapy.[24]

Compartment Syndrome: The Use of HBO for the Skeletal Muscle Compartment Syndrome is indicated in severe pain, marked swelling, tenseness of the muscle compartment, Neuropathy, myelopathy, and/or encephalopathy and Skeletal-Muscle compartment pressure measurements greater than 40 mmHg in the uncompromised host. Rising serial compartment pressure measurements as values approach 30-40 mmHg in mildly compromised host (diabetic, peripheral vascular disease, collagen vascular disease, etc.) and 20-30 mmHg in hypotensive patients will benefit from Hyperbaric Oxygen Therapy.[25]

D. Skin Grafts And Flaps (Compromised)

When the wound bed in skin grafts and flaps does not have enough oxygen supplied to it, the skin graft will at least partially fail. Common causes are previous radiation to the wound area, diabetes, and certain infections. Factors such as age, nutritional status, smoking etc, also result in an unpredictable pattern of blood flow to the skin. Partial or complete failure of the wound reconstruction is very difficult for a patient and also very expensive. HBO is well recognized for its role in assisting in the preparation and salvage of skin grafts and compromised flaps.[26]

E. Thermal Burns

The burn wound is a complex and dynamic pathophysiologic process characterized by a zone of coagulation, surrounded by a region of stasis, bounded by an area of hyperemia. Adjunctive HBO therapy has been shown to limit the progression of the burn injury, reduce swelling, reduce the need for surgery, diminish lung damage, shorten the hospitalization, and result in significant overall cost savings. These benefits are more apparent if therapy is initiated within 6-24 hours of the burn injury. Indications for HBO therapy include deep second-degree and third-degree burns that involve greater than 20% of the total body surface area, and less extensive burns that involve the face, hands or groin area.[27]

HBO In Oncology & Radiation Tissue Damage

Patients, who have received 2,000 to 5,000 rads or more, may have difficulties with any subsequent surgical healing. The primary mechanism of late radiation tissue complications is endarteritis (progressive loss of the microvasculature) resulting in tissue hypoxia, death and necrosis. Conventional treatment is often frustrating. Hyperbaric Oxygen is the only treatment available for these conditions and helps reduce morbidity, disfiguring sequelae and further need for corrective surgery. Hyperbaric Oxygen is also being evaluated for its role in enhancing radiosenstivity in selected head and neck tumors.

A. Late Radiation induced tissue damage

HBO raises tissue pO_2 to within the normal range initiating cellular and vascular repair mechanisms. It stimulates angiogenesis, increases neovascularization, fibroblast and osteoblast proliferation and collagen formation in hypovascular, irradiated tissues - skin, mucosa and bone. It thus helps in re-epithelialization of ulcers and creation of a vascular bed to support grafts and pedicle flaps. HBO is also bactericidal for certain anaerobes, bacteriostatic for certain species of escherichia and increases the rate of killing of bacteria by phagocytes thus helping immune suppressed patients.

Common indications are osteoradionecrosis, soft tissue necrosis, radiation cystitis, proctitis Enteritis, Vesicocutaneous fistula, radiation induced optic neuropathy, retinopathy, CNS damage etc.[28-30]

B. Adjunctive to therapeutic radiation

In an irradiated field, endarteritis, tissue hypoxia and tissue fibrosis occur leading to increased post operative complications like wound infections, dehiscence and delayed healing. Implantation of metal prostheses into irradiated tissue as restorative surgery give higher failure rate. Pre and post operative HBO enhances the quality of irradiated tissues to allow them to better withstand surgical insults. HBO stimulates bone formation, turnover and bone maturation. It significantly reduces the risk of osteo-radionecrosis and implants failure.

Prophylactic HBO is used for tooth extraction or surgery in previously irradiated tissue and prevention of Osseo integrated implant failures.[31]

C. Hyperbaric Oxygen as Radiosensitiser

The oxygen tension inside a tumor can be as low as 8 mmHg. It drops lower as the tumor enlarges and may drop to zero in the necrotic center of the tumor. Hypoxia increases the resistance of cancer to radiotherapy. With oxygen tension at zero, the amount of radiation required to be effective is three times that required with normal oxygen tension.

When irradiation is done immediately after HBO therapy, the well- oxygenated cells will be damaged lethally. The effect of HBO in enhancing radiosensitivity is most pronounced in head and neck tumors. HBO can be combined with other radiosensitivity enhancers too.

Indications are Neuroblastomas mainly Glioblastoma Multiforme and Astrocytoma and also Re-irradiation of squamous cell carcinoma head and neck.[32]

Hyperbaric Oxygen Therapy in Sudden Hearing Loss

Sudden hearing loss is a sensorineural hearing impairment, which develops over a period of few hours to a few days and with no recognized causes at the time of onset - cochlear ischemia is a frequent etiology. Studies have shown that cochlear activity is sensitive to constant supply of Oxygen and the performance of the auditory system can be improved by intense application of Oxygen alongwith vasodilators and anti-inflammatory drugs.

The beneficial effects of HBO on sudden sensorineural hearing loss are probably achieved by an increase in the distribution of O2 dissolved per volume unit of blood circulating through the regions affected by the lack of oxygen. Increase Oxygen in the peri and endolymph helps in the recovery of inner ear function. HBO also improves haemorrheology and contributes to improved microcirculation. It lowers hematocrit, blood viscosity and improves erythrocyte elasticity.[33]

Hyperbaric Oxygen Therapy in Air Embolism and Decompression Sickness

Air embolism may be caused by sudden decompression or ascent in diving, trauma like head and neck injuries, high altitude accidents or may be iatrogenic during a diagnostic or surgical procedure. Air emboli may lodge distally in the smaller arteries and arterioles of brain and obstruct the flow of blood resulting in ischemia, hypoxia and cerebral edema. The bubble may also act as a foreign body and start a number of chemical reactions.

Decompression Sickness (DCS) is caused by rapid reduction of environmental pressure, which may cause formation of bubbles from inert gases (mainly nitrogen) in the body tissues. Also humoral agents may be released from tissues secondary to trauma caused by expanding gas resulting in blood sludging. It may occur in divers, workers in compressed air tunnels or rapid ascent by an aviator (altitude DCS).

HBO is the first line of treatment in these conditions and helps by compression of bubbles by increased pressure and improves the diffusion of nitrogen from bubbles due to concentration gradient between bubble and surrounding tissues. HBO induced vasoconstriction inhibits air embolus redistribution and decreases cerebral edema. High O2 counteracts the ischemic and hypoxic effects of vascular obstruction. It also reduces blood sludging and improves WBC function.[34,35]

Hyperbaric Oxygen Therapy in Smoke Inhalation and Carbon Monoxide Poisoning

Smoke inhalation involves multiple toxicities, pulmonary insufficiency and thermal and chemical injuries. CO intoxication is the most immediate life-threatening disorder in such cases causing hypoxia resulting from displacement of oxygen from hemoglobin. CO poisoning involves most parts of the body but the areas most affected are those with high blood flow and oxygen requirement like brain and heart.

HBO causes immediate saturation of plasma with enough oxygen to sustain life and to counteract tissue hypoxia in spite of high levels of COHb. It causes a rapid reduction of CO in the blood and from cytochrome oxidase and restores its function. It also reduces cerebral edema and brain lipid peroxidation caused by CO.[36,37]

Hyperbaric Oxygen Therapy in Exceptional Blood Loss (Anemia)

If a patient has lost sufficient red cell mass to compromise respiratory requirements and will not receive transfusions because of medical or religious reasons, the intermittent use of hyperbaric oxygen therapy as short term management will supply enough oxygen to support the basic metabolic needs of the body until red blood cells are restored.

The following guidelines are recommended when using HBO in such indications: mean blood pressure below 60 mm Hg, or requirement for vasopressors; altered mental status; myocardial ischemia by clinical or ECG criteria; ischemic bowel or severe lactic acidosis.[38]

HBO In Research Indications (Neurology)

Evidence based Neurorehabilitation as a science is yet evolving, available treatment methods are not adequate and few centers have opportunity to explore the role of a range of modalities in these patients. After reviewing international and national experience a possible inference is that there appears evidence of a physiological basis and a possible role of Hyperbaric Oxygen in management of well-defined ischemic and anoxic neurological illnesses.[39]

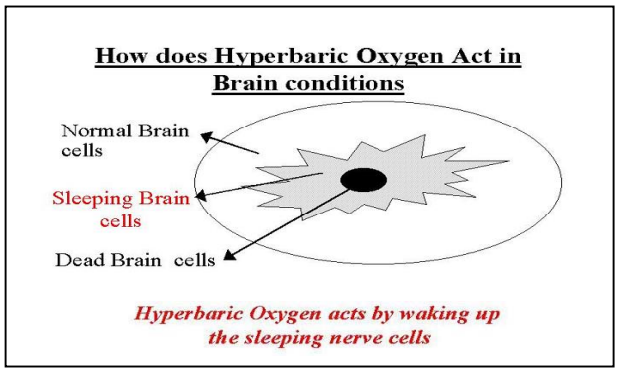

Fig. 1. ***Mechanism of action of HBO in Neurology***

Rationale for Hyperbaric Oxygen Therapy in the treatment of neurological illnesses

The rationale of use of Hyperbaric Oxygen in neurological indications is based on the finding in SPECT studies that around the central area of neuronal death is the penumbra: peri-infarct zone having hibernating/idling or sleeping neurons and gliosis (dead neurons) on CT scans may actually be viable tissue for years following the insult. HBO delivers high Oxygen to these "sleeping cells" and reactivates them. It also reduces edemas and reverses the reduced flexibility of erythrocytes. This is the basis of its use in acute stroke, post-traumatic brain injuries and cerebral palsy.[40]

Mechanism of action: The possible mechanism of action of HBO in neurological disorders is relief of hypoxia, improvement of microcirculation and cerebral metabolism, reduced cerebral edema by vasoconstrictive effect, increases the permeability of the blood-brain barrier and preservation of partially damaged tissue and prevention of further progression of secondary effects of cerebral lesions.

Indications for HBOT in neurological illnesses

Cerebrovascular accidents (stroke): The reported rate of improvement is 40% to 100%, which is much higher than the natural rate of recovery. It shows a striking reduction in spasticity possibly due to improved function of neurons in affected areas or the brain and secondly to rise of PO2 in the spastic inactive and hypoxic muscle. Additionally there is an improvement in the cognitive and mental performance. The major criticism is that none of the reported studies are random controlled.[41,42]

Acute traumatic brain injuries: HBO causes reduction of CBF thus reducing intracranial tension yet providing concomitant high doses of Oxygen to the brain. It interrupts the cycle of Ischemia, Hypoxia, edema and enzymatic derangements. There is improved aerobic metabolism, reduction in lactate levels, increase in creatinine phosphate and ATP levels. Elevation of partial pressure of Oxygen increases the diffusion distance, and O2 delivery in abnormal areas is enhanced. However there has to be a responsive cerebral circulation. It is contraindicated when a stage of vasomotor paralysis has developed, and must not have fixed and dilated pupils. Most favourable results are obtained in patients in mid level Glasgow Coma scales.[43]

Spinal cord injury: There is evidence that it is useful in Spinal cord traumas especially if administered within the first 4 hours and for subsequent rehabilitation of Spinal damage patients.[44]

Cerebral Palsy: Evidence now shows that HBO therapy may dramatically improve some CP symptoms – spasticity, vision, hearing, and speech. However improvement, if any, will vary from patient to patient. More oxygen may help many children with cerebral palsy, but it is NOT a cure. It is simply a way of ensuring the most complete recovery possible and must be combined with other therapies.[45,46,47]

Bell's Palsy: Steroids and surgical decompression are the only treatment used currently but results are inconclusive as to their benefit. HBO added to other treatment increases the efficacy of the treatment and reduces the period needed for restoration of complete function of the damaged nerve.[48]

Clinical Trials & Research Areas

A number of areas are being explored to determine if hyperbaric oxygen might be of clinical benefit. Senility, stroke, and are all being investigated. Sports Injuries, High Altitude Sickness, Brain Injury, Cognitive Functions, Migraine, Fulminant Hepatic Failure are also being actively researched. Sickle Cell Crisis, Spinal Cord Injury, Closed Head Injury. Purpura Fulminans, Actinomycosis, Mesenteric Thrombosis, Central Retinal Artery Occlusion, Cystoid Macular Edema, and Leprosy are other areas being explored by workers in multicentric trials the world over. Other areas being addressed are designs of Randomized clinical trials, Placebo effect, Hawthorne effect, Pharmokinetics etc.[3,49]

CONCLUSION

Hyperbaric Medicine is poised at an exciting era of revival. The role of Hyperbaric Oxygen Therapy is "evidence based" in certain well defined conditions and the Hyperbaric Chamber is now an integral part of hospital services. Doctors in all fields must familiarize

themselves with recent evidence on this mode of therapy, so that their patients are not denied the gains of this modern treatment. Cost analysis has shown that the addition of Hyperbaric Oxygen to conventional treatment results in significant cost savings due to lesser stay in hospital and shorter course of illness.

REFERENCES:

1. Leach R M, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. BMJ 1998; 317:1140-1143.
2. Gabb G, Robin ED. Hyperbaric oxygen: a therapy in search of disease. CHEST 1987; 92 :1074 -82.
3. Hampson NB. Chairman & Editor. Hyperbaric Oxygen Therapy: 1999 Committee Report. Kensington MD: Undersea & Hyperbaric Medical Society 1999.
4. Grim PS, Gottlieb LJ, et al. Hyperbaric oxygen therapy (review). JAMA 1990; 263(16):2216-20.
5. Tibbles PM, Edelsberg J S. Hyperbaric Oxygen Therapy (Review article). NEJM 1996; 1642-1648.
6. TK Sahni, MJ John, AM Madhwal et al. Hyperbaric Oxygen Therapy in Hospital Practice. Bombay Hospital Journal 1993; 35(4):59-64.
7. Bassett BE, Bennett PB. Introduction to the physical and physiological basis of hyperbaric therapy .In: Davis JC, Hunt TK Ed., Hyperbaric Oxygen Therapy, Kensington MD: Undersea & Hyperbaric Medical Society 1986: 11-24.
8. Sahni T, Singh P, John MJ. Hyperbaric Oxygen Therapy: Current Trends And Applications. JAPI 2003; 51:280-284.
9. Edmonds C, Lowry C, Pennefather J. Oxygen toxicity. In: Diving and Subaquatic Medicine 3rd ed. Oxford: Butterworth - Heineman Ltd. 1994: 241-256.
10. Van Den Brenk , The hazards of Oxygen toxicity in a Hyperbaric Environment. In: GS Innes Ed., The production and hazards of a Hyperbaric Oxygen Environment. London: Pergamon Press, 1970:49-54.
11. Boykin VJ. Hyperbaric Oxygen therapy: A physiological Approach to selected Problem Wound healing. Wounds 1996; 8(6):183-198.
12. Cohn GH. Hyperbaric oxygen therapy - promoting healing in difficult cases. Postgraduate medicine1986; 79(2): 89-92.
13. Kindwall EP, Gottlieb FJ, Larson DL. Hyperbaric Oxygen therapy in Plastic Surgery, Plastic and Reconstructive therapy 1991; 888(5): 898-908.
14. Urayama H, Takemura H, Kasajima F, et al. Hyperbaric Oxygen therapy for chronic occlusive arterial diseases of the extremeties. Journal of Japanese Surgical Society 1992; 93(4): 429-33.
15. Cramer FS. Care of the Injured Soldier: A medical Readiness role for Clinical Hyperbaric Oxygen Therapy. Medical Corps International 1990.5(2): 36-40
16. Ballard JL, Eke CC, Bunt TJ, Killen JD. A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. J Vasc Surg 1995; 22:485-490.
17. Bunt TJ, Holloway GA. TcPO2 as an accurate predictor of therapy in limb salvage. Ann Vasc Surg 1996; 10:224-227.
18. DJ Bakker. The use of Hyperbaric Oxygen in the treatment of certain infectious diseases especially gasgangrene and acute dermal gangrenes. Wageninger : Drukkerij Veenam 1984
19. Calhoun JH, Cobos JA, Mader JT. Does Hyperbaric Oxygen have a place in the treatment of Osteomyelitis? Orthopedic Clinics of North America 1991; 22(3): 467-71.
20. TenheyJE, DavisJC, Workman WT. Hyperbaric Oxygen Therapy. Orthopedic Review 1987; XIV (11): 829-833
21. Riseman JA, Zambons WA, Curtis A, et al. Hyperbaric Oxygen for necrotising fascitis reduces mortality and need for debridements. Surgery 1990; 108(5): 847-50.
22. Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P. Hyper baric oxygen therapy in the management of crush injuries: A randomized double-blind placebo-controlled clinical trial. J Trauma 1996; 41:333-339.
23. Gustilo R, Williams DN. The use of antibiotics in the management of open fractures. Orthopedics 1984; 7:1617-1619.
24. Johansen K, Daines M, Howey T, Helfet D, Hansen ST Jr. Objective criteria accurately predict amputation following lower extremity trauma. J Trauma 1990; 30:568-573.
25. Barlett RL, Stroman RT, Nickels M, Kallns JE, Fuhrman CT, Pipemeier EH. Rabbit model of the use of fasciotomy and hyperbaric oxygenation in the treatment of compartment syndrome. Undersea Hyper Med 1998; 25(suppl):29.
26. Zamboni WA. Applications of hyperbaric oxygen therapy in plastic surgery. In: Oriani G, Marroni A, Wattel F, eds. Handbook on hyperbaric oxygen therapy. New York: Springer-Verlag, 1996
27. Cianci P,Sato R. Adjunctive hyperbaric Oxygen Therapy in the treatment of thermal burns: a review. Burns 1994:20(1) 5-14.
28. Marx RE, et al. Radiation injury to tissue. In: E. P. Kindwall. Ed., Hyperbaric Medicine Practice. FlagStaff AZ: Best Publishing Co. 1994; 447-504
29. Dempsey J, et al. Cost effectiveness analysis of hyperbaric therapy in osteoradionecrosis. Can J Plast Surg 1997; 5(4): 221-229
30. Feldmeirer JJ, Heimbach RD, Davolt DA et al. Hyperbaric Oxygen and the cancer patient, a survey of practice patterns. Undersea and Hyperbaric Medicine1993; 20 (4): 337-345.
31. Feldmeier JJ, Newman R, Davolt DA, Heimbach RD, Newman NK, Hernandez LC. Prophylactic hyperbaric oxygen for patients undergoing salvage for recurrent head and neck cancers following full course irradiation. Undersea Hyper Med 1998; 25(Suppl):10.
32. Koshi K, Kinoshita Y, Imada H et al. Effects of radiotherapy after hyperbaric oxygenation on malignant gliomas. Br J Ca 1999; 80:236-241.
33. Lamm K, Lamm H, Arnold W. Effect of hyperbaric oxygen therapy in comparison to conventional or placebo therapy or no treatment in idiopathic sudden hearing loss, acoustic trauma, noise-induced hearing

loss and tinnitus. A literature survey. Advances in Otorhinolaryngology 1998; (54): 86-99.
34. Catron PW, Dutka AJ, Biondi DM et al. Cerebral Air Embolism treated by Pressure and Hyperbaric Oxygen. Neurology 1991; 41(2): 314-5.
35. Davis JC.Elliot DH. Treatment of the decompression disorders. In: Bennett PB, Elliot DH. Ed.,The physiology and medicine of Diving .3rd Ed. San Pedro : Best Publishers .1982 : 473 - 486
36. Norkool DM, Kirkpatrick JN. Treatment of acute carbon monoxide poisoning with hyperbaric oxygen: A review of 115 cases. Ann Emerg Med 1985; 14:1168-1171.
37. Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. Anaesth Intens 1992; 20:311-316.
38. Hart GB. Exceptional Blood loss anemia treatment with Hyperbaric Oxygen. JAMA 1974; 228:1028-1029.
39. Sahni T, Jain M. Status of Status of Hyperbaric Oxygen Therapy in Neurological Illnesses – Review of International and Indian experience. Neurosciences Today 2003; 7:126-134.
40. Astrup J, Sazio BC, Simon. Threshold of Ischemia: The Ischemic Penumbra. Stroke 1981: (12): 723-5.
41. Soodan KS; Roy AK; PK Singh et al. Hyperbaric Oxygen Therapy in Stroke cases .Ind J Aerospace Medicine1992; 36 (1): 28 - 3.
42. MalikD,Gomez G. Hyperbaric Oxygen therapy: Our experiences at 1 AMTC. Ind J Aerospace Med 1999:43 (1): 18 –23.
43. Rockswold GL, Ford SE et al. Results of a prospective randomised trial for treatment of severely brain injured patients with Hyperbaric Oxygen. J of Neuro Surgery 1992; 76(6): 929-34.
44. Asamoto S, Sugiyama H, Doi H, et al. Hyperbaric oxygen (Hbo) therapy for acute traumatic cervical spinal cord injury. Spinal Cord 2000; 38(9): 538-540.
45. Montgomery D, Goldberg J, Amar M et al. Effects of hyperbaric oxygen therapy on children with spastic diplegic cerebral palsy: A pilot project. Undersea Hyperb Med. 1999 Winter; 26(4): 235-42.
46. Harch PG. McGill University Pilot Study of HBOT in the Treatment of Spastic Diplegia Cerebral Palsy. Hyper Med Today, August-September, 2000; 1(3): 44-45.
47. Collet JP, Vanasse M et al. Hyperbaric oxygen for children with cerebral palsy; a randomized multicentre trial. HBO-CP Research Group. Lancet 2001; 357(9256): 582-86.
48. Heiden CH, Biesinger E, Hoing R. Idiopathic facial palsy (Bell's Palsy): an indication for hyperbaric oxygen therapy? Eur J Underwater Hyper baric Med 2003; 4(1): 20-23.
49. KK Jain. Ed.,Textbook of Hyperbaric Medicine .2nd Ed. Toronto : Hogrefe & Huber Publishers. 1996.