Personal Practice

ROLE OF HYPERBARIC OXYGEN THERAPY IN ONCOLOGY AND RADIATION INDUCED TISSUE DAMAGE

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Cancer treatment has improved significantly over the past decade and there is an ongoing focus on not only finding more and better ways to treat cancers but also to improve quality of life of the cancer survivor. One-half of the estimated 1.2 million new cases of invasive cancer will receive radiation therapy as a part of their cancer treatment and despite best efforts, 5% of patients will develop severe reactions to radiation therapy.

The goal of radiation therapy is to eradicate tumors with minimal, if any, adverse effects. However despite preventive measures permanent damage may occur. This leads often, to painful and disabling conditions. Conventional treatment of these lesions often has frustrating results.

Hyperbaric Oxygenation (HBO) has been proposed as a part of the overall treatment since the mid 1960s and several studies have reported beneficial effects. Hyperbaric oxygen helps reduce morbidity, disfiguring sequelae and further need for corrective surgery. It is also being evaluated for its role in enhancing radiosenstivity in selected head and neck tumors.

This article reviews the role of Hyperbaric oxygen in the management of cancers and the sequalae of side effects due to radiation.

Key words: Hyperbaric oxygen, Oncology, Radiation complication, Radio sensitizer.

SURGERY, radiation therapy and cytotoxic chemotherapy are the principal methods employed in the treatment of cancer. Radiation therapy differs from the other two modes of treatment in that its most serious associated morbidity tends to occur months or years after treatment when management is often difficult and unsatisfactory.

Because a dominant feature of post-radiation change is the obliteration of small blood vessels leading to hypoxia, hyperbaric oxygen has been employed in the care of these patients. In the past forty years there have been many publications reporting benefit in studies, which have included some thousands of patients.

INCIDENCE OF THE RADIO-INDUCED LESIONS IN NORMAL TISSUES

A large number of cancer patients receive radiation as part of their treatment. The incidence figures of radio-induced chronic lesions vary widely according to definition and site. Despite best efforts, 5% of patients develop severe reactions to radiation therapy often leading to painful and disabling conditions. Of these, about 1% may have serious problems, requiring major surgery and prolonged hospital care. Personal and social problems may be very distressing and commonly those affected are unable to pursue gainful employment.

The risk factors for development of late radiation morbidity are similar over all sites and include the total radiation dose, the overall time, the biological effective dose which takes into account fraction size and the overall time, the volume irradiated, the use of a combination of external beam with an implantation or intracavitary procedure, a high dose rate with brachytherapy, tumours adjacent to or involving bone, the presence of infection, the use of surgery and the occurrence of trauma. Patients, who have received 2,000 to 5,000 rads or more, may have difficulties with any subsequent surgical healing. "Conformal" radiotherapy has encouraged the attainment of higher tumour doses and inevitably some normal tissues will be included. The concomitant administration of cytotoxics where an adjuvant effect is likely to increase the incidence of late damage and the quantitative importance of these drug radiation interactions are difficult to predict. An increasing use of major surgery for restoration of function or for salvage of advanced recurrent disease is also associated with a high risk of morbidity when a heavily irradiated area is operated upon.

TISSUE CHANGES INDUCED BY RADIOTHERAPY

The main underlying mechanism of radio-induced chronic lesions is endarteritis - a progressive loss of the

microvasculature resulting in tissue hypoxia, death and necrosis. When heavily irradiated tissues are examined at an interval of months or years after treatment the characteristic findings are a cellular depletion, fibrosis and a reduction in vascular density with marked narrowing of the small blood vessels. Molecular biology has shown that hypoxia could trigger altered gene expression leading to a whole range of effects. Severe cases usually require surgical removal of the necrosed tissue.

Conventional treatment of these lesions often has frustrating results. 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 radiosensitivity in selected head and neck tumors.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (HBO) is a form of treatment in which a patient breathes 100% oxygen while inside a special treatment chamber. The pressure in this treatment chamber is increased to higher than normal atmospheric pressure and the patient then breathes oxygen at this higher pressure. Most treatment is carried out at twice the atmospheric pressure and no significant side effects are documented. With continuing growth all over the world Hyperbaric medicine has found a distinct role in the modern era of evidence-based medicine.

PHYSIOLOGICAL BASIS OF HBO THERAPY

When we normally breathe air (with 21% O_2) at sea level pressure, most tissue needs of Oxygen are met from the O_2 combined to Hb, which is 95 % saturated 100 ml blood carries 19 ml O_2 combined with Hb and 0.32 ml dissolved in plasma. At this same pressure if 100% O_2 is inspired, O_2 combined with Hb increases to a maximum of 20 ml and that dissolved in plasma to 2.09 ml. The higher pressure during Hyperbaric oxygen treatment pushes more Oxygen into solution. The amount of O_2 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 O_2 in solution is almost sufficient to meet tissue needs without contribution from O_2 bound to hemoglobin and is responsible for most of the beneficial effects of this therapy [1,5](*Table* 1).

Table 1. Effect ofpressure on arterial O_2.

Total pressure		Contents 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 HbO_2 capacity of blood is 20 vol %.

THERAPEUTIC EFFECTS OF HBO_2 THERAPY

1. Hyperoxygenation causes: (i) Immune stimulation by restoring WBC function and enhance 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.

2. **Vasoconstriction** reduces edema and tissue swelling while ensuring adequate Oxygen delivery and is thus useful in acute trauma wounds and burns.
3. **Bactericidal** for anaerobic organisms and 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.
4. **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.
5. **Mechanical effects:** Direct benefit of increased pressure helps reduces bubble size in Air embolism and Decompression illnesses.
6. **Reactivates "sleeping cells" in the penumbra** region around central dead neuronal tissue and is the basis of use in neurological conditions. It also reduces adherence of WBCs to capillary walls and may be useful in acute brain and spinal cord injury.

INDICATIONS FOR HYPERBARIC OXYGEN IN ONCOLOGY

1. HBO in the management of radionecrosis (radiation induced chronic lesions)

Physiological basis

HBO raises the 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 stimulates collagen formation at wound edges and thus helps in re-epithelialization of ulcers and provides a better nutritive 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.

Indications

- *Osteoradionecrosis:* Most commonly mandibular necrosis.
- *Soft tissue necrosis:* Laryngeal, head and neck, chest wall necrosis, extremeties.
- Radiation cystitis, Radiation proctitis and enteritis.
- Other abdominal and pelvic injuries (vagina, pelvic bone, groin).
- Radiation induced optic neuropathy.
- Radiation induced retinopathy.
- Vesicocutaneous fistula.
- Central nervous system.

2. HBO as an adjunctive therapy to therapeutic radiation

Physiological basis

In a previously irradiated field, endarteritis, tissue hypoxia and tissue fibrosis may occur leading to increased post operative complications like wound infections, dehiscence and delayed wound healing. Also, implantation of metal prostheses into heavily irradiated tissue as restorative surgery in patients who have extensive resections give higher failure rate. Preoperative HBO enhances the quality of tissues to allow them to better withstand the surgical insults. HBO in experimental studies has been shown to stimulate bone formation, increase bone turnover and especially bone maturation. It significantly reduces the risk of osteo-radionecrosis and implant failure

Indications

- Reduction of risk of radionecrosis in tooth extraction or surgery in previously irradiated tissue.
- Prevention of surgical complications in reconstructive surgery.
- Prevention of osseointegrated implant failures.

3. HBO as a radiosensitizer

Physiological basis

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 centre 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

- Neuroblastomas • Glioblastoma multiforme
  • Astrocytoma
- Re-irradiation of squamous cell carcinoma head and neck

HBO AND CARCINOGENESIS

There is some concern that tumor angiogenesis is likely to be promoted by hyperbaric oxygen in the same fashion that angiogenesis is promoted in non-healing hypoxic wounds. However, these are very different physiologic and pathophysiologic systems. The available published evidence strongly suggests that intermittent hyperbaric oxygen has no enhancing effect on cancer primary or metastatic growth. The possibility that significant immune suppression, free radical induced damage or mutations leading to carcinogenesis is likely to enhance malignant growth in hyperbaric patients is also not well supported by literature. Large numbers of mostly controlled studies including over 3,000 patients demonstrate either a neutral or cancer inhibitory effect.

COST EFFECTIVENESS OF HYPERBARIC OXYGEN THERAPY

Serious late radiation complications frequently require surgery within the irradiated field where the likelihood of postoperative complications is about 50%. By either avoiding surgery or supporting surgical healing, HBO therapy can significantly reduce the financial and human costs of radiation complications.

CONCLUSION

HBO is a safe therapy with very few and minor side effects. The successful use of HBO in the treatment of radio-induced tissue lesions will reduce morbidity, disabling or disfiguring sequelae and further need for corrective or demolitive surgery. Addition of HBO obviates the need for frequent surgical procedures, promotes healing and early mobilization of the patient. It reduces length of hospitalization and thereby overall treatment and rehabilitation costs. In some specific malignant cancers the addition of Hyperbaric oxygen as an adjunct to radiotherapy may lead to significantly higher cure rates.

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