

HYPERBARIC OXYGEN THERAPY RESEARCH (Auckland, NZ)

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Hyperbaric oxygen therapy has been used in human medicine for nearly 100 years. The first common usage was for divers suffering from decompression sickness, but now there is a wide range of applications in both human and veterinary medicine including healing of problem wounds, treatment of traumatic brain injury and as an adjunct to treatment of spinal cord trauma. The patient enters a hyperbaric chamber which is then pressurized over approximately fifteen minutes to two BAR absolute (2 BAR) or higher. 100% oxygen is breathed throughout the treatment which usually lasts for 90 minutes including fifteen minutes of decompression. Patients rarely need sedation and usually go to sleep for the duration of the treatment. There is a video camera so observation of the patient is possible. Multiple treatments (usually a course of five 90 minute sessions) are necessary, depending on the condition being treated, and treatment as an outpatient is possible. Three chambers are available for animal use in New Zealand, one at the Veterinary Specialist Group in Auckland, one in Richmond, Nelson and one in Tauranga.

There is little high quality scientific evidence available thus far in the form of randomized, controlled and double blinded studies to support the use of hyperbaric oxygen therapy (HBOT), however some does exist. A good resource at www.hboevidence.com brings together some meta-analyses on the use of HBOT in various conditions; systematic reviews at www.cochrane.org also contain an impartial summary of the evidence available in each area and can be found using “hyperbaric oxygen” as the search term. A local website at www.o2vet.co.nz has further information about HBOT in New Zealand. The fact that evidence has not been published for many applications does not necessarily mean that it does not work. HBOT is used every day in both human and veterinary medicine for an increasingly wide range of conditions with good results. HBOT is an area of active research in human medicine in the areas of stroke and radiotherapy in particular, and new evidence as to efficacy is rapidly continuing to accumulate.

Oxygen used in the therapeutic context is a drug, and as with any other drug the efficacy and safety depend upon the dose used. The use of HBOT has developed empirically over a long period of time and the dosages used have been mostly derived from trial and error. “Dose” in hyperbaric oxygen therapy (HBOT) is determined by the pressure used (up to 4ATA have been used for some disease syndromes), by the duration of each session, the frequency with which they take place and length of time treatment is given for. The efficacy of HBOT may well continue to improve as our understanding of mechanisms of action and skill in its use improves.

There are two main aspects to the benefits derived from treatment; the mechanical effects of increased pressure and the physiological effects of improved oxygenation to the tissues.

Hyperbaric pressure reduces the size of bubbles both in blood vessels and tissues. This is of obvious relevance to decompression illness - the pain of “the bends” is derived from bubbles in tendons. Iatrogenically introduced air such as might occur during surgical and medical procedures can also be treated with HBOT; the increased pressure reduces bubble length in the vessel and reduces ischaemia.

Situations which benefit most from hyperbaric delivery of oxygen are those where transport of oxygen to the tissues or the ability of the tissues to use the oxygen delivered is compromised. These situations can occur with poisonings, trauma, metabolic disease such as diabetes causing microvascular compromise and skin flaps and free grafts. Capillaries may be crushed, transected or vasoconstricted, or oedema may compress the microvasculature preventing oxygen from being delivered via normal blood bound transport. Hypoxia is undesirable as it depresses mitochondrial oxidative phosphorylation and causes a decline in ATP level. Most (97%) of the oxygen in arterial blood is usually transported bound to haemoglobin. 3% is dissolved in the plasma itself. With increasing pressure increasing amounts of oxygen are dissolved into the plasma, significantly improving tissue oxygenation and allowing aerobic respiration in the absence of haemoglobin bound oxygen transport. The oxygen dissolved in the plasma also leaves the capillaries more readily than haemoglobin bound oxygen. Hyperbaric oxygenation allows oxygen to diffuse from the capillaries into the tissues four times as far as normobaric oxygenation. Tissue oxygen tension remains elevated for up to 3 hours following a one hour HBOT session. HBOT contributes to increased perfusion by reducing platelet aggregation and improving the membrane pliability of the red blood cells. High arterial oxygen tensions may have an osmotic effect, relieving oedema by promoting fluid re-absorption to the vascular compartment.

The effect HBOT has on blood vessels depends on their local microenvironment. In the brain, hypoxia causes an increase in nitric oxide synthase production and vasodilation. A vicious cycle begins, in which vasogenic oedema causes a reduction in blood flow and overall cerebral blood volume increases as a result, causing an increase in intracranial pressure and further impedance to blood flow. Hyperoxia induces the production of free radicals such as superoxide anions which inhibit nitric oxide synthase production and thus reduce vasodilation and oedema in healthy tissue. Hyperoxia may damage healthy organs; the vasoconstriction which occurs is one of the body’s protective mechanisms to prevent damage from excessive pO₂. This vasoconstrictor response does not usually take place in hypoxic tissues. This phenomenon has been shown in one study in skin. Dermal blood flow as measured by laser Doppler flowmetry decreased in response to hyperoxia. The authors of this study also demonstrated that reduction of blood flow did not occur in the area of a chronic skin ulcer but that the vasoconstrictor response was restored after the ulcer had healed.

Restoration of normal tissue oxygen tension allows a return to normal function and contributes to healing in a number of different ways. Oxygen itself is an antibacterial agent; it is also synergistic with some other antibiotics and enhances the innate host immune response both by providing energy required for phagocytosis and by acting as a substrate for the production of reactive oxygen species such as the superoxide anion and hydrogen

peroxide used in the respiratory burst. The quantity and quality of collagen formed is improved, and the matrix formed acts as structural support for newly forming blood vessels. Endothelial migration and function has been shown to increase with HBOT and epithelialisation is also enhanced.

Whereas normoxia stimulates the immune system, hyperoxia suppresses immune and inflammatory responses such as leucocyte activation and subsequent binding to injured epithelium; this may be helpful in some situations such as reperfusion injury and sepsis. This is the basis of using HBOT in crush injuries, compartment syndrome and disseminated intravascular coagulation (DIC).

Most of the recent research in human medicine has focused on this role of HBOT in modulating the inflammatory response. Hyperbaric oxygenation has been shown to inactivate the enzyme cyclo-oxygenase, and also plays a role in intracellular signalling and gene expression. It acts in a number of ways to improve microcirculatory perfusion, modulate cytokine production, reduce nitric oxide synthase expression, affect adhesive molecules such as ICAM-1 and induce the expression of antioxidant enzymes. Prevention of leucocyte activation is the first step in prevention of ischaemia-reperfusion injury and subsequent lipid peroxidation. The prevention of the secondary injury mechanisms triggered by hypoxia, lipid peroxidation and cell membrane damage may be one way that HBOT can contribute to healing from acute spinal trauma.

So far at the Veterinary Specialist Group we have treated approximately thirty patients since July 2008. Most of these have been treated as an adjunct to spinal surgeries such as a ventral slot or hemilaminectomy. Some medicine patients such as a diabetic cat with a non-healing abscess and an immunosuppressed dog with multiple skin wounds have also had the benefit of treatment. One of the first patients treated was "Rex", a one year old male crossbreed Shih Tzu, who had been hit by a car on a Saturday night. He came in to the Animal Emergency Centre on Sunday from the referring veterinarians for overnight monitoring and handover to the VSG surgery service on Monday morning.

On Monday he was assessed as having a proptosed left eye that would require removal and a complete comminuted open fracture of the mid-distal right tibia and fibula. The plan was to place a circle fixator, however when the bandage was removed after the induction of anaesthesia there was oedema and bite wounds to the thigh musculature and a large wound was seen on the medial side of the tibia with frank purulent discharge. Radiographs showed extensive bacterial gas production throughout the lower limb. Given the degree of bacterial load and severity of the comminuted open fracture it was decided to perform a proximal third femoral amputation rather than attempt fixation and risk uncontrolled bacteraemia. Surgery was performed the same day. Triple antibiotics were given and his first hyperbaric oxygen session took place the following day. Rex improved rapidly and was discharged several days later with oral pain relief and antibiotics. Four months after surgery his owners report he is leading a full and active life. He loves being out and about, jumping on and off the farm bike and herding the cattle on the family farm with the rest of the dogs.

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