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The role of hyperbaric oxygen therapy in trauma

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This review explains the method of action of hyperbaric oxygenation (HBO) therapy and examines the evidence for its use in trauma. Methods of delivery, complications and contra-indications are discussed. It is acknowledged that there are few controlled trials which evaluate the efficacy of HBO in this indication; supporting evidence for its efficacy is mainly in the form of case reports, or by implication from laboratory and animal work. Lack of evidence may not equate to lack of efficacy, but may reflect the difficulties in coordinating clinical trials involving critically ill patients and a complex treatment modality, the availability of which is not widespread. The adjunctive use of HBO has shown promising results in the treatment of crush injury. Consideration of tissue pathophysiology suggests that such an approach may also offer improved outcomes in the broader spectrum of trauma scenarios involving marginally viable tissues with compromised perfusion.

Key words: hyperbaric oxygenation; trauma; crush injury; compartment syndrome; gas gangrene; necrotising fasciitis; burns

Definition of hyperbaric oxygenation

Hyperbaric oxygenation (HBO) therapy is defined as a treatment in which the patient breathes 100% oxygen at pressures greater than atmospheric (Buettner and Wolkenhauer, 2007). Breathing high concentrations of oxygen at surface pressure, and the topical exposure of limbs to high concentrations of oxygen, are excluded by this definition. It must be emphasised that an adequate circulation is required for oxygen delivery; HBO therapy does not imply absorption of oxygen through the skin.

Indications

In 1976 the Undersea and Hyperbaric Medical Society (UHMS), concerned at the exaggerated claims being made for the efficacy of HBO, promulgated a list of indications for which there was sufficient evidence to justify the re-imbursement of the costs of HBO treatment. The list undergoes regular revision as new evidence emerges. The currently recommended indications (UHMS, 2008) are:

- Decompression sickness
- Air or gas embolism
- Crush injury and compartment syndrome
- Clostridial myositis and myonecrosis
- Thermal burns
- Enhancement of healing in problematic wounds
- Compromised skin grafts and flaps
- Exceptional blood loss
- Intracranial abscess
- Necrotising soft tissue infections
- Refractory osteomyelitis
- Carbon monoxide poisoning
- Delayed radiation injury (soft tissue and bony necrosis)

Mechanisms of action of HBO therapy

The effects of HBO therapy can be explained in terms of UHMS mechanical and gaseous effects.

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Mechanical effect

This concerns the reduction in volume of gaseous bubbles within the blood and tissues in response to increased ambient pressure (Boyle's Law). This effect is used therapeutically to treat decompression illness and gas embolism. In both these conditions, gases come out of solution to form bubbles which may cause direct tissue damage; in the circulation they may cause arterial occlusion. Compression reduces their size and aids their passage through the vascular tree. These pathologies commonly arise in diving casualties, though air embolism may also be iatrogenic, relating to the use of intravascular lines. They will not be discussed further in this review.

Gaseous effect

This is of greater interest to the traumatologist. When air is breathed at sea-level pressure, oxygen is carried within the body bound to haemoglobin at saturation levels of 97%, yielding an arterial oxygen tension of 100 mmHg, with 0.3 mL oxygen/100 mL dissolved in plasma. Due to the sigmoid shape of the oxygen–haemoglobin dissociation curve, increased flows of oxygen at surface pressure achieve little change in the saturation of haemoglobin. The volume of oxygen dissolved in plasma, however, has a linear relationship with alveolar oxygen and rises in proportion to the increased alveolar partial pressure (Henry's law). When the oxygen partial pressures approaches 100%, as are commonly administered to the trauma victim, the dissolved oxygen concentration rises to approximately 2 mL/100 mL of oxygenated blood (Rowe, 2001). HBO treatment takes this process further. In an atmosphere of 100% oxygen at 3 ATA (atmospheres absolute) equating to sea-water pressure at 20 m depth, ambient oxygen pressure is 2280 mmHg, yielding arterial oxygen tensions approaching 2000 mmHg. At this pressure, 6 mL oxygen/100 mL blood is dissolved in the plasma, representing a 20-fold increase in unbound oxygen (Bao, 1987).

This gaseous effect is of particular relevance to the treatment of traumatic injuries which, despite many different presentations, share common features at the level of the micro-circulation. Direct trauma to blood and lymphatic channels causes fluid accumulation in the interstitium. Inflammatory pathways additionally increase capillary permeability, resulting in vasogenic oedema of the interstitial space (Buettner and Wolkenhauer, 2007). The interstitial pressure rises in response and there is compression of the thin-walled venous outflow, favouring further fluid accumulation. The distance across which oxygen must diffuse from cells to capillaries thus increases. In traumatic wounds, some degree of oedematous hypoxia is therefore inevitable (Myers, 2000). This further compromises perfusion to tissues, which may already be hypoxic, following capillary damage and consequent blockage to the circulation of erythrocytes. In the face of significant hypoxia, intracellular supplies of ATP are eventually exhausted, as shown in Figure 1. This leads to failure of the sodium pump responsible for active transport of sodium from intracellular fluid. The rise in intracellular sodium concentration is accompanied by an influx of chloride; intracellular

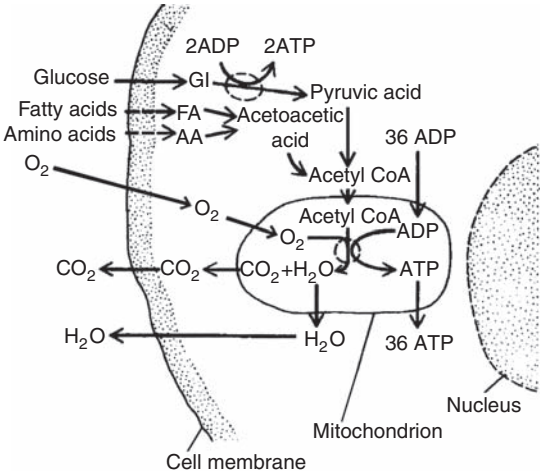

Figure 1 Substrates and products of glycolysis

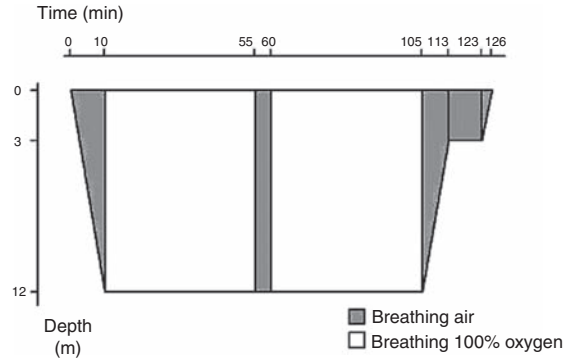

Figure 2 Hyperbaric treatment profile

osmotic pressure rises and prompts an influx of water and cytogenic oedema (Bao, 1987). A vicious cycle develops in which ischaemic tissue becomes oedematous at both intracellular and extracellular levels, thus increasing the likelihood of further hypoxia (Jain, 2004), and creating a situation whereby traumatised tissue tends to be progressively more hypoxic at the centre (Malerba *et al*., 1996).

Hyperoxia promotes reversal of this pathology via the inter-related mechanisms of hyperoxygenation, vasoconstriction and oedema reduction. At the cellular level, hyperoxia promotes angiogenesis and enhances leucocyte and fibroblast activity.

(a) Hyperoxygenation

The distance of oxygen diffusion through tissue fluids is proportional to the square root of the oxygen concentration in the source capillary (Rowe, 2001). At 2 ATA pressure, the diffusion distance of oxygen through tissue fluids is increased by a factor of three (Kindwall *et al*., 1991). HBO thus makes possible the delivery of oxygen to hypoxic tissues beyond the reach of normobaric oxygenation, so restoring ATP pump function.

(b) Vasoconstriction

Oxygen at partial pressures greater than 500 mmHg causes vasoconstriction (Bookspan, 2000) through contraction of smooth muscle vasculature. This is estimated to cause a 20% reduction in limb blood flow (Bird and Telfer, 1965). Any decrease in oxygen delivery attributed to vasoconstriction is more than offset by the increased oxygen tension (Kindwall *et al*., 1991). Vasoconstriction is mainly an arterial effect, with tissue outflow and lymphatic drainage largely unaffected (Strauss, 1981; Shupak *et al*., 1987).

(c) Oedema reduction

Following arterial vasoconstriction, the fall in capillary hydrostatic pressure reduces capillary transudation and favours reabsorption from the interstitium. The net effect is a reduction of tissue oedema (Strauss *et al*., 1987). Although it has been demonstrated that tissue oxygen tensions return to normal within 3 h of an HBO session (Wells *et al*., 1977), the effects upon oedema are prolonged. Following the creation with tourniquet of experimental ischaemia in the hind limb of the rat, and using the contra-lateral limb as control, treatment with HBO (2.5 ATA, 45 min, single session) has been reported to achieve a significant reduction in post-ischaemic oedema ($p < 0.001$) for 40 h (Nylander *et al*., 1985).

In traumatised hypoxic tissue, HBO not only tackles symptomatic hypoxia by delivering more oxygen, but also addresses the cause of hypoxia by reducing the volume of the oedematous tissue. The cycle of oedema-hypoxia-vasodilation may thus be interrupted and potentially reversed.

(d) Enhanced cellular function

In well-perfused, normally oxygenated tissue, HBO treatment confers no benefit to wound healing (Kindwall *et al*., 1991). The diminished perfusion of traumatic wounds, however, renders them liable to hypoxia, precisely when there is an increased demand for oxygen from processes involved in wound repair. These processes are oxygen dependent and may increase cellular oxygen requirements 20-fold (Strauss, 1986). In hypoxic conditions angiogenesis is slowed (Wang *et al*., 2002). In oxygen tensions below 30 mmHg, fibroblast function is degraded – since the hydroxylation of proline to procollagen is oxygen dependent (Hunt and Pai, 1972) – and collagen formation is compromised. Hyperoxia helps reverse these deficits, enhancing angiogenesis (Manson *et al*., 1980) and stimulating fibroblast proliferation and collagen synthesis (Hunt *et al*., 1977). Lack of oxygen also renders wounds liable to infection; when partial pressures fall below 30 mmHg, as is common in traumatised tissue (Kindwall *et al*., 1991), leucocyte function is compromised (Malerba *et al*., 1996). HBO therapy enhances the oxygen-dependent, intracellular-killing capability of leucocytes (Tibbles and Edelsberg, 1996) by providing substrate for the formation of oxygen free radicals and augmenting the oxidative respiratory burst (Clark and Moon, 1999). The combination of these effects leads to increased rates of wound closure in hypoxic tissues (Kivisaari and Niinikoski, 1975).

HBO in crush injury, compartment syndrome and thermal burns

These conditions may be considered together in that they share a common pathophysiology involving ischaemia, hypoxia and oedema, a tendency for

these features to become self-perpetuating as noted above, and a gradient of ischaemia across the injured tissues (Myers, 2000). At the point of injury, damaged tissues are devitalised and non-viable. Intervention here should be surgical, aimed at adequate removal of necrotic tissue. Between this zone of tissue destruction, and the healthy tissues at the rim of the wounded area, lie tissues that have suffered varying degrees of damage and which may be prone to secondary ischaemic insult in the aftermath of the initial injury. This may arise from large vessel thrombosis, but is more often due to microvascular ischaemia prompted by oedema, stasis, tissue fluid pressure and vascular occlusion (Buettner and Wolkenhauer, 2007). The development of compartment syndrome is an extreme example of this phenomenon. HBO treatment is directed at this middle zone of variably injured tissue with the aim of minimising secondary insult and maximising the preservation of healthy tissue.

Crush injury

The value of such an approach is well illustrated in crush injuries which, in addition to soft tissue trauma, may also involve fracture, neurological injury and vascular compromise. Surgery is employed to repair or stabilise these structures. In cases complicated by broken bones, fracture stabilisation is an immediate priority, yet the timing and method of fixation must take into account the need to minimise further damage to traumatised and potentially ischaemic tissue. Intramedullary devices and external fixators both limit further damage to periosteal vasculature, with incisions performed away from the site of injury. This recognised need to maximise perfusion should also favour treatment with HBO.

The best evidence for the use of HBO therapy comes from a controlled trial performed by Bouachour *et al*. (1996). Based upon the injury classification of Gustilo *et al*. (1984), and following initial surgery within 6 h, 36 cases of grade two or three crush injury were randomised within 24 h of surgery to either treatment with HBO (100% O_2 at 2.5 ATA for 90 min, twice daily for 6 days), or sham hyperbaric treatment (21%O_2 at 1.1 ATA, identical treatment schedule). The two groups were similarly treated with antibiotics, anticoagulants and wound dressings and were similar in respect of age, co-morbidities and injury patterns. Results showed that 17 patients achieved complete healing in the HBO group, compared to ten in the sham group ($p < 0.01$). Following blind reassessment, six patients in the sham group, but only one patient in the treatment group required a second surgical intervention ($p < 0.05$). Sub-group analysis revealed that the addition of HBO had been especially effective in patients aged over 40 with grade three injuries. In this sub-group, there were seven successes and one failure in the HBO group, but three successes and seven failures in similarly aged patients treated with sham therapy ($p < 0.005$). For HBO therapy to achieve the above benefits there must be adequate arterial flow (Bouachour and Cronier, 1996). In cases of macro-vascular injury, arterial repair must precede consideration of HBO therapy.

Compartment syndrome

In compartment syndrome, pressures in skeletal muscle compartments are sufficiently raised to reduce or halt vascular in flow and for this reason, prompt surgical decompression is the first accepted treatment to restore tissue perfusion. Fasciotomy may be performed entirely on clinical grounds, or in response to a compartmental interstitial pressures greater than 30 mmHg absolute, or within 30 mmHg of the diastolic pressure. Yet, following inadvertent calf compression and intra-operative hypotension, intra-compartmental calf pressures in excess of 35 mmHg bilaterally are reported to have been controlled by prompt HBO treatment without the need for fasciotomy (Van Poucke *et al*., 2001). In another series, ten symptomatic patients were treated with HBO when compartment pressures were elevated between 15 and 48 mmHg, but before surgery was indicated. All the patients recovered without the need for surgery (Strauss and Hart, 1989). It is not suggested that HBO therapy should replace fasciotomy in established cases. Yet in presentations where compartment syndrome is a risk, the early addition of HBO into the standard care of repeated examination and pressure readings may prevent progression. No trials have been performed into this pre-operative indication. In the post-fasciotomy phase, however, the potential for preservation of marginally ischaemic tissue

provide good reason for considering adjunctive treatment (Greensmith, 2004).

Thermal burns

The same rationale for HBO treatment apply in cases of thermal burns. In a previous study, the mean length of hospital stay in 16 patients with burns of 18–39% body surface area was reduced from 33 days in the control group to 21 days in patients receiving HBO as adjuvant treatment (Cianci *et al*., 1989). In patients with 40–80% burns, the number of operations required was reduced from eight to four in patients receiving adjuvant HBO and matched for age and burn characteristics (Cianci *et al*., 1988). Unless HBO facilities become incorporated within burns' centres, however, the need to minimise the movement of critically ill patients requires that burns' patients be treated in a recognised burns unit. This remains the current UHMS recommendation.

HBO in gas gangrene

Gas gangrene is a fulminating myonecrotic infection with Gram-positive anaerobic bacilli of the species *Clostridium*, notably *Clostridium perfringens*. The majority of cases are the consequence of contamination of traumatic wounds, where tissue damage has resulted in locally hypoxic tissue, thus allowing *Clostridium* to thrive (Malerba *et al*., 1996). Myonecrosis is caused by an alpha-toxin produced by the bacterium. This is not only haemolytic but also has phospholipase activity, with consequent hydrolysis of phospholipids and activation of arachidonic acid inflammatory pathways causing increased vascular permeability. Direct tissue damage and increased permeability prompt tissue oedema (Sakurai *et al*., 2004), which in turn contributes to further hypoxia, hence facilitating multiplication of the bacteria.

Surgical management with antibiotic therapy should constitute the first line of management. At tissue oxygen tensions in excess of 250 mmHg, alpha-toxin production is halted (Cohn, 1986). This occurs within minutes of commencing HBO therapy (Bakker, 1988). In animal studies, the combination of HBO and surgery has been demonstrated to be synergistic in reducing morbidity and mortality (Stephens, 1996). These findings have been replicated in humans, where a case series has reported that with HBO the need for extensive debridement and amputation is significantly reduced, and that viable and non-viable tissue is more strongly demarcated, thus facilitating more accurate tissue debridement (Hart and Strauss, 1990). It is therefore proposed that in cases of gas gangrene, the initial surgical management should be limited to fasciotomy, with debridement of the necrotic tissue performed later, after treatment with HBO (Cohn, 1986). The extent of ablation may be reduced if early HBO treatment is used to halt progression of the infection.

HBO in necrotising fasciitis

These fulminant, synergistic infections are characterised by the presence of mixed bacterial species. The general benefits of HBO still apply, though unlike its specific action against *Clostridium*, HBO in this instance has no specific action against infecting bacteria beyond the enhancement of leucocytic action noted above. Initial treatment should be surgical, comprising early, thorough debridement, followed by antibiotic therapy. Adjunctive HBO treatment may be instituted later. No controlled trials have been reported which examine the use of HBO in this indication, though meta-analysis of clinical cases supports its use (Clark and Moon, 1999). It may be specifically considered in patients with high-risk perineal or truncal infection, or those who respond poorly. When used in this way, a mortality reduction compared to controls of 66–23% has been reported, with a reduced need for ablative surgery (Riseman *et al*., 1990). Urgent referral of those failing to respond to surgery and antibiotics within 48 h has been suggested (MacFarlane *et al*., 2000).

HBO in fracture healing

The evidence which examines the effect of HBO in this application comes only from laboratory and animal studies. HBO enhances osteoclast activity (Barth *et al*., 1990) and is synergistic with bone morphogenic protein in promoting bone healing (Okubo *et al*., 2001). In a study of bone healing in

rabbits, which had undergone tibial lengthening, HBO was associated with an increased bone mineral density in the treated group (Ueng *et al*., 1998). A Cochrane systematic review of 2005 found, however, that no conclusive controlled trials have been performed, and that there was consequently no clinical evidence, either to support or to refute the treatment of fractures with HBO (Bennett *et al*., 2005).

Delivery of HBO therapy

Treatment may be delivered in a monoplace chamber, in which a single patient is accommodated in a pressurised cylinder, now generally made of acrylic material to permit patient observation. The cylinder is pressurised entirely with oxygen. In this environment the patient cannot be accompanied. Patients such as trauma victims requiring higher levels of care can alternatively be treated in multiplace chambers, with attendants, full monitoring and ventilatory support. In chambers of this size, for reasons of safety, the ambient gas is compressed air, with patients breathing 100% oxygen through masks or hoods.

Other than for treatment of diving accidents, HBO treatment sessions are generally conducted at pressures of 2-2.4 ATA, incorporating 90 min of oxygen exposure, as shown in Figure 2. In order to minimise the risk of oxygen toxicity, periods breathing 100% oxygen are separated by brief intervals of breathing air.

In cases of acute soft tissue trauma, one or two sessions per day are envisaged, over a period of up to 1 week, and maybe beyond, depending on tissue response. Individual treatments are decided by the hyperbaricist in conjunction with the operative surgeon.

Complications and contra-indications of HBO therapy

Complications

The side-effect profile of HBO therapy is mostly benign. The commonest complication is the mechanical effect of middle ear barotrauma. This is not a bar to further treatment if myringotomy tubes are placed. The risks of burst lung and air embolism, which are more common in the diving environment, are very much minimised in hyperbaric practice where rates of decompression are strictly controlled. Nonetheless, care should be taken in cases of obstructive respiratory disease and treatment may be contraindicated if the risk of air trapping is severe. Mild cases may be successfully treated with prolongation of the decompression phase.

With regard to gaseous effects, oxygen is a potent drug at increased partial pressures. Adherence to proven treatment profiles is essential. Cerebral oxygen toxicity, leading to seizures, is a rare but potentially serious complication associated with the possibility of air trapping during decompression in a patient who is not ventilating normally. Sensitivity is variable, both between and within individuals. The overall incidence is reported as 1.3/10,000 treatments (Davis *et al*., 1988). With prolonged courses of HBO, patients are prone to myopic shift which, in the great majority of cases, corrects spontaneously in the weeks following treatment.

Contra-indications

(a) Relative

Sinusitis

- Inability to equalise pressure in the middle ear (may require myringotomy)
- Claustrophobia
- History of pneumothorax
- Thoracic surgery and chronic obstructive airways disease, which are associated with an increased risk of burst lung and air trapping
- History of fitting, which may be associated with a lower threshold to seizures from oxygen toxicity (Bookspan, 2000).

(b) Absolute

Untreated pneumothorax.

- Ongoing treatment with chemotherapeutic agents. Anthracyclines such as doxorubicin exert their tumoricidal effects through the generation of free radicals. Their cytotoxicity is exacerbated by oxygen exposure. The concomitant use of HBO and cisplatinum confers a high risk of impaired wound healing.

– Any history of treatment with bleomycin. This agent poses a lifelong risk of susceptibility to oxygen toxicity.

Summary

There is evidence that adjunctive HBO therapy offers improved outcomes in a range of trauma scenarios, principally those in which marginally viable tissues may be salvaged by early reduction of oedema, increased perfusion and by maximising tissue oxygenation. Crush injury is a prime example of a pathology in which a benefit from HBO treatment has been clinically demonstrated. In other indications, it is recognised that there is a lack of grade one evidence to support the use of HBO therapy. This may not represent a lack of efficacy, but rather reflect the difficulties inherent in establishing high quality, blinded trials using a complex treatment modality, the availability of which is not widespread. Although HBO would appear to offer benefit in certain indications, the critical nature of these conditions prevents the transfer of patients to remote units; until HBO facilities become available closer to intensive care units it is unlikely that the potential benefits will be explored.

Treatment with HBO is expensive; at the time of writing, typical charges for a single routine treatment range from £130 to £200, with considerably higher charges for emergency work. Against this, the financial benefits arising if the casualty returns to employment should be set. Further studies, encompassing both efficacy and cost effectiveness, are urgently required.

Further information on the availability of hyperbaric treatment within the UK is available from the British Hyperbaric Association via the Association's website, www.hyperbaric.org.uk

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