The physiological role of adjuvant hyperbaric oxygen therapy in trauma management and rehabilitation

A systematic review of the literature comparing the therapeutic uses of hyperbaric oxygen therapy in trauma beyond its' original clinical application

Introduction

Major trauma is a devastating health problem, accounting for 20,000 hospital admissions and 5,400 deaths in England alone\(^1\). Mortality and morbidity mainly result from diminished perfusion caused by damaged vasculature, and increased cellular oxygen demand\(^2\) which combine to create severe oxygen debt. The resultant hypoxia presents a major difficulty in trauma management, where the reductions of these effects are a priority.

Pathophysiology of trauma

Direct trauma to vasculature and lymphatics cause fluid accumulation in the interstitium. Inflammatory pathways activated by the traumatic insult increase capillary permeability, causing vasogenic oedema in the interstitial space\(^3\). With the expanding fluid, interstitial pressure rises, compressing low pressure venous outflow, accentuating further oedema.

Vasogenic oedema increases cellular oxygen diffusion distances, compromising perfusion and creating localised oedematous hypoxia. Significant hypoxia causes depletion of aerobically dependent ATP stores (see figure 1). The absence of ATP causes intracellular sodium pumps to fail resulting in intracellular sodium build-up with accompanying potassium and chloride influx. The additional osmotic

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Figure 1. Illustration of sodium potassium pump
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pressure this causes increases cytogenic oedema and creates a vicious cycle of oedematous hypoxia on already ischaemic tissue.\(^4\)

**Hyperbaric oxygenation**

**Definition**

Hyperbaric oxygenation (HBO\(_2\)T) occurs when the patient breathes in 100% oxygen (O\(_2\)) at pressures exceeding that of the atmosphere.\(^3\) High concentration oxygen at atmospheric level, and localised exposure of affected limbs to oxygen does not qualify as hyperbaric oxygenation, so are excluded in this review.

**Physiological rationale for HBO\(_2\)T action**

HBO\(_2\)T promotes the reversal of the pathophysiology of trauma via the following mechanisms:

i. **Increased oxygen diffusion.**\(^5\)

The distance of oxygen diffusion through fluid is proportional to the square root of oxygen concentration in the capillary. At 2 times the atmospheric pressure (2 ATA), the diffusion distance oxygen can accomplish is trebled. The physiological relevance is that oedematous hypoxic tissues can receive oxygen at diffusion distances greater than normobaric oxygenation.

ii. **Vasoconstriction.**\(^6\)

High partial pressures of oxygen exceeding 500 mmHg causes vasoconstriction, mainly of the arteries, increasing venous outflow relative to arterial inflow. This decreases capillary transudation into the interstitium, and so decreases oedema. There is also an approximate 20% decrease in limb blood loss, with the decreased blood supply offset by increased oxygen tension.

iii. **Enhanced cellular function.**\(^7\)

Hyperoxia promotes angiogenesis and stimulates fibroblast and collagen synthesis, enhancing healing. HBO\(_2\)T therapy has also been shown to enhance aerobic leucocyte activity, which reduces the common complication of infection in trauma.

**Current and future indications**
The current indications for HBO₂T use are under constant review by the Undersea and Hyperbaric Medical Society (UHMS) as new evidence emerges for future indications. Its current recommended uses as of UHMS, 2011⁸ are shown in Box 1.

This review will focus on the following recommended indications: Compartment syndrome, thermal burns, acute blood loss, fracture healing and traumatic brain injury.

**Methodology**

Preliminary reading and discussion of the subject was conducted at the Hyperbaric Medical Facility, Isle of Man⁹ (IOM) and the Keyll Darree Medical Library at Nobles Hospital, IOM. The review was conducted through the University of Liverpool website using Scopus, PubMed and Discover archives.

Randomised controlled studies were preferred and where unavailable, non-randomised controlled, observational and case report studies were included.

**Rationale, review of clinical evidence and discussion for adjuvant HBO₂T in trauma**

**Compartment syndrome**

Following trauma, pressures in skeletal muscles may rise sufficiently to cause vascular stasis, resulting in oedematous hypoxia and ischaemia. If interstitial pressure rise over
30mmHg, a Fasciotomy is performed to relieve pressure and restore tissue perfusion\textsuperscript{10}. HBO\textsubscript{2}T is therefore physiologically indicated due to its anti-oedematous and hyperoxygenative properties.

Prompt HBO\textsubscript{2}T therapy being effectively used to control post-surgical intra-compartmental calf pressures exceeding 35 mmHg\textsuperscript{11}; this effect was also noted despite intra-operative hypotension also being reported, suggesting, although an isolated event, that HBO\textsubscript{2}T therapy may be effective in sub-adequate blood flow. A further case series\textsuperscript{12} identified 10 patients who recovered with Fasciotomies following symptomatic compartment syndrome from compartment pressures ranging between 15-48 mmHg.

It is not suggested by the UHMS that HBO\textsubscript{2}T should replace fasciotomy is clinically established cases. However if HBO\textsubscript{2}T is used prophylactically, in situations where compartment syndrome is a risk, such as surgery, it may reduce the incidence of post-operative compartment syndrome. As yet no trials have been conducted into this clinical indication, but this suggests a direction for future research.

**Thermal burns**

Burns activate the inflammatory cascade, causing vasodilation and increased vascular permeability. This fluid shift from intravascular to extravascular spaces causes hypovolaemia and localised oedema. It is therefore an indication to use HBO\textsubscript{2}T, due to its vasoconstrictive and anti-oedematous actions.

A retrospective study\textsuperscript{13} found that the length of hospital stay in 16 patients with between 18-39\% burns was significantly reduced from 33 days in the control group (n=8) to 21 days in the adjuvant HBO\textsubscript{2}T group (n=8) (p=0.05). 24 patients with 40-80\% burns receiving adjuvant HBO\textsubscript{2}T therapy required half the number of operations (4 vs 8) compared to those receiving only the standard treatment\textsuperscript{14}.
While these results are encouraging, unless HBO₂T services become incorporated in burns centres, the risk of moving critically ill patients from major burns units, where their clinical need is greatest, to hyperbaric chambers is likely to be too great.

**Haemorrhage**

Managing blood loss remains the foremost challenge in trauma. Decreasing blood stocks, autoimmune rejection and disease transmission risk creates a need for alternatives. The hyperoxygenating and vasoconstrictive effect of HBO₂T as a temporalising measure for hypoxic tissue is an interesting direction.

A randomised controlled trial¹⁵ of HBO₂T use on 41 patients with haemoglobin levels <90 g/L found that 30% increased their levels of hepatic venous oxygen saturation (ShvO₂). Serum lactate levels were also significantly decreased, which reflects decreased anaerobic respiration.

These results are encouraging, and suggest that HBO₂T could be used as an adjuvant to minimise blood transfusions, or even replace transfusions in non-critical scenarios of blood loss. However until facilities are in place to safely treat actively haemorrhaging patients in hyperbaric chambers, blood transfusions will still be favoured.

**Fractures**

The treatment of fractures centres on re-establishing the structural integrity of bone, and restoring function to the traumatised area. Fracture healing is impaired by poor vascularity, infection and loss of soft tissues¹⁸. As already discussed, the potential for HBO₂T therapy in promoting angiogenesis, enhancing leukocyte function and promoting soft tissue repair makes it an interesting adjuvant therapy for fractures.

There a paucity of clinical trials carried out on humans with HBO₂T in fractures. A recent study has found an increased production of bone morphogenic cytokines involved in fracture healing¹⁹, which is encouraging. While these trials suggest potential in HBO₂T
therapy, the lack of randomised trials conducted on humans is limiting. There are currently three ongoing randomised controlled trials\textsuperscript{21-23} to investigate HBO\textsubscript{2}T therapy in fracture healing. Until these are complete, there is insufficient clinical evidence to support or disprove the treatment of fractures with HBO\textsubscript{2}T.

**Traumatic brain injury**

The brain consumes 20\% of total systemic oxygen, and, due to few energy reserves, is dependent on a good oxygen and glucose supply. It is therefore most vulnerable to hypoxia secondary to a traumatic brain injury (TBI). While no effective treatment for TBI exist, managing secondary brain injury is essential to reducing mortality and morbidity. Secondary injury involves tissue hypoxia, inflammation and resulting cerebral oedema. HBO\textsubscript{2}T has been shown to be effective in high altitude cerebral oedema\textsuperscript{24}, and the ability of HBO\textsubscript{2}T to correct tissue hypoxia, inflammation and therefore cerebral oedema makes it an interesting and exciting adjuvant therapy for prevention of secondary TBI.

These studies demonstrate the impact HBO\textsubscript{2} therapy can have on reducing mortality and morbidity. Going forward, a recent trial\textsuperscript{27} has demonstrated HBO\textsubscript{2}T inducing significant brain function improvements, as seen in Figure 2, in 56 patients following mild TBI.

**Side-effects and contraindications of HBO\textsubscript{2}T**

The side effect profile of HBO\textsubscript{2}T means it should not be treated as completely benign. The most common complications are middle ear barotrauma due to fluctuating atmospheric pressure. Cerebral oxygen toxicity is a rare (incidence due to HBO\textsubscript{2}T are
1.3/10,000) but potentially serious complication. However, if rates of decompression are prolonged and strictly controlled, then this risk can almost be reduced to almost zero\textsuperscript{28}.

The only absolute contraindication is an untreated pneumothorax. Where there is polytrauma, particularly including the chest, pneumothorax must be ruled out or treated before HBO\textsubscript{2}T. If a chest drain is correctly inserted, the risk is reduced to almost zero\textsuperscript{28}.

**Conclusion and areas for future research**

The evidence for adjuvant HBO\textsubscript{2}T is compelling at this early stage, suggesting it has a future role in trauma management and rehabilitation.

This review makes no attempt to specify ideal timings or pressures for treating the individual traumatic insults discussed. In the studies, the specific pressures either were not recorded or conflicted between studies, so few inferences of optimal hyperbaric regimen could not be discerned. This is an essential direction for future research, as the diverse clinical indications may have differing optimal pressures.

The review does not apply any economic evaluation to HBO\textsubscript{2}T. Any future research into efficacy and cost effectiveness are essential in assessing HBO\textsubscript{2}T viability.

*Further information regarding HBO\textsubscript{2}T in the UK is available from the British Hyperbaric Association at www.hyperbaric.org.uk.*
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