Hyperbaric oxygen therapy in the management of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts and crush injury

A West Midlands Development and Evaluation Service Report

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West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the effectiveness of hyperbaric oxygen therapy in the treatment of carbon monoxide poisoning; osteoradionecrosis; burns; skin grafts and crush injury was:

***Carbon monoxide poisoning - Not Supported**
Osteoradionecrosis - Not Proven
Burns - Not Proven
Skin grafts - Borderline
Crush injuries – Borderline

*However it should be noted that much of the evidence provided related to non-comatose patients and may not be generalisable to those in a comatose state.

Anticipated expiry date: 2005

- This report was completed in March 2000
- The searches were completed in December 1999
- A major double blinded randomised controlled trial is currently being completed and interim results suggest that it is unlikely that the conclusion of this report will alter during the next five years.

Question addressed by this review:

Is hyperbaric oxygen therapy (HBO_2) effective in the treatment of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts and crush injury?

Conclusion:

While HBO_2 is widely accepted as the appropriate treatment for gas embolism and decompression sickness, there is no convincing evidence that it is of benefit for the treatment of carbon monoxide poisoning (severe or moderate), osteoradionecrosis, burns, skin grafts or crush injury. However there is a physiological case for an effect of HBO_2 in conditions involving hypoxia such as osteoradionecrosis and wound healing. An extension of this review to include all controlled trials on wound healing would be warranted

West Midlands Development & Evaluation Service

The West Midlands Development and Evaluation Service (DES) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

West Midlands DES is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Contribution of Authors

Patrick Saunders undertook the collection and collation of evidence for this review. Jackie Young and Chris Hyde gave advice on the formulation of the question and overall process of the review, helped with some of the writing and structuring of the report and read and commented on the draft report.

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Conflicts of Interest

This work has been undertaken by staff funded by the NHS. The author has received no funding from any sponsor in this work.

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Abbreviations and Acronyms

atm abs	Atmosphere Absolute
BHA	British Hyperbaric Association
COHb	Carboxyhaemoglobin
DES	Development and Evaluation Service
DNS	Delayed Neurological Symptoms
ECHM	European Committee for Hyperbaric Medicine
EEG	Electroencephalogram
HBO	Hyperbaric Oxygen
HBO_2	Hyperbaric Oxygen Therapy
LOS	Length of Stay
NBO	Normobaric Oxygen
NBOT	Normobaric Oxygen Therapy
RCT	Randomised Controlled Trial
UHMS	Undersea and Hyperbaric Medicine Society

Summary

Hyperbaric oxygen therapy involves the intermittent inhalation of 100% oxygen under pressures greater than one atmosphere absolute.

The therapy can provide benefit due to the physical effects of hyperbaric oxygen on gasses and the hyperoxia that the treatment produces.

However, while there is a consensus on the value of the treatment for decompression sickness and air embolism there is controversy over the many other claims made for the therapy.

This review has focussed on five conditions and has identified 13 randomised controlled trials, six on carbon monoxide poisoning, two on osteoradionecrosis, three on burns, one on skin grafts and one on crush injury.

While hyperbaric oxygen therapy is an appropriate treatment for gas embolism and decompression sickness, there is no convincing evidence that it is of benefit for the treatment of carbon monoxide poisoning (severe or moderate), osteoradionecrosis, burns, skin grafts or crush injury. However there is a physiological case for an effect of hyperbaric oxygen therapy in conditions involving hypoxia such as osteoradionecrosis and wound healing.

1 Introduction

While there has been some controversy for many years regarding the use of hyperbaric oxygen (HBO) in the treatment of a number of conditions, specific concerns were raised in the West Midlands in the late 1990s for three principal reasons. Firstly, an apparent cluster of accidental carbon monoxide poisonings in North Staffordshire Health Authority led to queries regarding the cost of the HBO treatments involved.[1] Secondly, the Department of Public Health and Epidemiology at the University of Birmingham developed a research interest in the epidemiology of carbon monoxide poisoning following the involvement of departmental staff in the management of the North Staffordshire incidents [1; 2] and thirdly, a number of Accident and Emergency consultants expressed an interest in the clinical and business case for a HBO Unit in the West Midlands region. This review has been conducted to determine whether such a case exists.

2 Background

2.1 Nature of the intervention

Hyperbaric oxygen therapy (HBO_2) involves intermittent inhalation of 100% oxygen under pressure greater than one atmosphere absolute (atm abs). The Undersea Hyperbaric Medicine Society (UHMS) has defined HBO_2 as the application of 100% oxygen at pressures greater than 1.4 atm abs.[3] The HBO chamber may be single or multiplace or occasionally duoplace. In the monoplace unit, a single patient lies supine and there is only limited access to the patient. However, this type of chamber is cheaper and more portable than the multiplace chamber where the oxygen is administered to the patients in large pressurised tanks accommodating between two and fourteen people via tight fitting masks or hood tents. The additional room in the multiplace chamber allows staff to treat the patient for other problems.[4] (See figures 1 and 2).

Figure 1 - Monoplace Unit

Figure 2 - Entrance to Multiplace Unit

The pressure inside the chamber is usually increased to 2.2-2.8 atm abs (equivalent to a depth of 14-18m of water) although in the treatment of air embolism and decompression sickness where pressure is critical to therapeutic effect, treatment may start at higher pressures.[5] Treatment periods vary widely (45 to 300 minutes) and patients may receive up to 40 sessions depending on the condition.[4]

The physical effects of HBO on gases substantiate its use in the treatment of decompression sickness and air embolism. Two basic physical laws apply; Boyle's law and Henry's Law. Boyle's law (PV = kT (P = pressure, V=volume, k=constant, T=temperature)) states there is an inverse relationship between the pressure and volume of an ideal gas. If, for example, a diver at 66 feet of seawater (3 atm abs) running out of air takes one last deep breath before ascending too quickly, the air in his lungs will rapidly expand as the pressure decreases. This can potentially rupture the lungs or air may be directly insufflated into a pulmonary vein, return to the left side of the heart and then onward to the brain resulting in a cerebral air embolism. Henry's law (C = kP where C is the molar concentration of the dissolved gas, P is the pressure of the gas over the solution and k is the Henry's Law constant) states that the amount of an ideal gas in solution is directly proportional to the partial pressure of the gas. The nitrogen in solution in a rapidly ascending diver's blood will come out of solution and form bubbles in the circulation and tissue. Clearly increasing pressure as in HBO_2 will result in any bubbles being reduced in size and as the inert gas within the bubble is replaced with oxygen subsequently metabolised by the tissues, dissolution of the bubble should occur more rapidly.[6; 7]

The additional pressure combined with high levels of oxygen associated with HBO_2 increases the level of oxygen dissolved in the blood plasma.[5] At 3 atm abs, dissolved oxygen in blood is approximately 60 ml/L which adequately supplies resting need without drawing on haemoglobin. Leach has identified the following cellular benefits of this hyperoxia (although many of the data have been obtained under normobaric conditions):[4; 8]

- promotion of angiogenesis and wound healing;
- destruction of some anaerobes;
- prevention of the growth of some organisms e.g. C.perfringens;
- prevention of the production of clostridial alpha toxin;
- restoration of neutrophil mediated bacterial killing in previously hypoxic tissues;
- reduction of leucocyte adhesion in reperfusion injury and therefore the likelihood of vasoconstriction and cellular damage.

In addition to the treatment of decompression sickness and air embolism, HBO_2 has also been used in treating a variety of other conditions over the last 40 years with often little regard to the quality of evidence for its value. This has led to considerable scepticism regarding claims made for the therapy which continues to be used even for conditions such as multiple sclerosis and dementia where it has been demonstrated as having no value.[4; 6]

The European Committee for Hyperbaric Medicine (ECHM) advocates HBO_2 for the first line treatment of the conditions listed in table 1[9]:

Air or gas embolism
Decompression illness
Carbon monoxide poisoning
Gas gangrene
Necrotising fasciitis
Post-radiotherapy tissue damage
Preparation for surgery in previously irradiated tissue

Table 1 - ECHM Conditions for first line treatment by HBO

The UHMS also recommends HBO_2 for the treatment of the additional conditions given in table 2[9]:

Crush injury
Severe haemorrhagic anaemia
Selected problem wounds
Compromised skin flaps and grafts
Refractory osteomyelitis
Osteoradionecrosis
Thermal burns

Table 2 - UHMS Recommended Conditions for HBO in addition those of the ECHM

HBO_2 has also been used for a bewildering range of other conditions (see table 3).

Table 3 - Various Indications Used for HBO Treatment during the Past Few Decades

Radiation necrosis	Lyell's syndrome
Decompression sickness	CO poisoning
Gas embolism	Gas gangrene
Soft tissue infection, due to mixed aerobic and anaerobic organisms	Osteomyelitis (refractory)
Soft tissue necrosis	Crohn's disease
Bacteroides infection	Cyanide poisoning
Compromised skin grafts or flaps	Crush injury with traumatic ischaemia
Fungal infections	Alzheimer's disease
Mucormycosis	Brain oedema
Anaemia from exceptional blood loss	Thermal burns
Carbon tetrachloride poisoning	Head and spinal injury
Fractures	Bone grafts
Lepromatous leprosy	Frostbite
Meningitis	Cerebrovascular accidents
Radiation myelitis, cystitis, enteritis	Hydrogen sulfide poisoning
Retinal artery insufficiency	Cancer therapy
Chronic brain ischaemia	Pseudomembranous colitis
Senility	Sickle cell crisis
Multi-infarct dementia	Multiple sclerosis
Infant cardiac surgery	Pyoderma gangrenosum
Chronic ulcers	Acute myocardial infarction
Peripheral vascular disease	Carotid aneurysm
Diabetic neuropathy	Aortic aneurysm
Acute endocarditis	Anaerobic infections
Hearing loss due to acoustic trauma	Postcardiac surgery
Cortical blindness	Pulmonary insufficiency
Cellulitis	Arteriosclerosis
Infected pacemaker	Causalgia
Hurler's syndrome	Collagen vascular diseases
Postcardiac arrest	Postoperative confusion
Scleroderma	Traumatic amputation
Mycobacterium tuberculosis	Pulmonary emboli
Abscess, intraabdominal intracranial	Drowning
Asthma	Moyamoya
Pneumomediastinum	Surgical empyema
Hanging	Pharyngeal fistula
Thrombophlebitis	Brain cyst
Necrotizing fasciitis	Stenotic valvular heart disease
Postepileptic headaches	Tetanus
Radiation pneumonia	Intestinal obstruction
Balloon aspiration	Viral encephalitis
Migraine	Bites
Allergic reaction	Buerger's disease
Quadriplegia	Vascular headache

Dust-induced bronchitis	Precardiac surgery
Gastroduodenal ulcer	Tracheal fistula
Facial neuritis	Vertigo
Late pregnancy toxaemia	Rheumatoid arthritis
Liver failure	Preservation of youthfulness
Closed chest trauma	Viral hepatitis
Emphysema	Habitual abortion
Paralytic ileus	Sodium nitrite poisoning
Rendu-Osler Weber disease	Diabetes mellitus
Perirectal fistula	Fourier's gangrene
Necrobiosis lipoidic diabeticorum	Acute pancreatitis
Black lung disease	Organophosphate poisoning
Allergies	Perianal hidradenitis supprativa
Myositis	Organ preservation
Colitis	Muscular dystrophy
Cerebral vasospasm	Poor circulation
Malignant otitis externa	Cirrhosis of the liver
Acute hearing loss	Epilepsy
Pneumatosis cystoides intestinales	Pulmonary hypertension
Maxillofacial phlegmon	Lung lavage
Cochlear vesibular syndrome	Revascularization
Periodontosis	Chronic coronary artery disease

Adapted from Gabb and Robin [10]

The British Hyperbaric Association (BHA) identifies 25 member hyperbaric chambers in the UK (see **figure 3**). These are operated by Hospital Trusts, Government Agency, St John's Ambulance, the Police and as private enterprises. There are no facilities within the West Midlands region although there are proposals to develop one.

Figure 3 – Location of BHA Chambers in the British Isles (1998)

2.2 Risks of HBO_2

It is generally accepted that if the pressure is below 3 atm abs and duration of treatment is less than 120 minutes, HBO_2 is safe.[4] The most common fatal complication of HBO_2 is due to fire, which can be catastrophic in the confined space of a chamber. Fires are generally caused by prohibited sources of ignition brought in by the patient.[11] An analysis of such fires for the period 1927 to 1996 identified 77 human fatalities in 35 hyperbaric fires.[11] In 1997, a fire in a chamber in Milan, Italy killed ten patients and a nurse. Ten years previously in Naples, a spark from a toy gun brought into a single place chamber by a four year-old child caused a fatal fire.[12]

Severe central nervous system symptoms occur in 1-2% of treated patients, symptomatic reversible barotrauma in 20-40%, pulmonary symptoms in 15-20% and reversible optic symptoms in up to 20% of patients [4] although these figures have been challenged as overestimates.[8; 13] As there are relatively few HBO_2 chambers, transport over long distances may be required. This carries risks of its own and will, of course, extend the time between exposure and treatment. Leach has described the risks of HBO_2 (see table 4).[4]

Table 4 - Complications of HBO

Fire
Claustrophobia
Reversible myopia
Fatigue
Headache
Vomiting
Barotrauma
• ear, sinus and lung damage
• ruptured middle ear
Oxygen toxicity
• convulsions
• pulmonary oedema
• haemorrhage
• respiratory failure
Decompression illness
• decompression sickness
• pneumothorax
• gas emboli

With large numbers of sessions (>90) the formation of cataracts has been reported.[3] The most important contraindication for HBO_2 is untreated pneumothorax. Other potential contraindications include upper respiratory infections, bullous emphysema and claustrophobia.[14] Chronic obstructive lung disease is not necessarily in itself a contraindication as there are reports of severe cases being treated with no problems.[3] HBO_2

should also be avoided after cardiopulmonary resuscitation with external chest compression.[15] Rarely, acute pulmonary oedema can be caused in patients with heart failure.[3]

2.3 Prevalence and Incidence of Key Conditions

Tables 5 and 6 show the number of patients receiving HBO_2 and the conditions treated at UK facilities.

Table 5 – Number of patients receiving hyperbaric therapy at BHA chambers

	1994	1995	1996	1997
Diving related emergencies	262	270	258	349
Hyperbaric oxygen emergency cases	315	343	385	352
Hyperbaric oxygen elective cases	346	425	639	673

(The British Hyperbaric Association. Register of Member Chambers 1998)[9]

In the years 1994-1997 the demand for HBO_2 increased mainly due to an increase in the number of patients receiving elective treatment. Treatment for diving related conditions has remained stable and there was some increase in the number of patients receiving emergency HBO_2 unrelated to diving. This was predominantly for carbon monoxide poisoning.[9]

Table 6 – Indications for hyperbaric therapy in patients treated in 1997 at BHA chambers

	Number of Patients	% of Patients
Decompression illness	349	25.4
Carbon monoxide poisoning	352	25.6
Gas embolism (non-diving)	0	0
Soft tissue infections	32	2.3
Post radiotherapy	112	8.2
Other ECHM or UHMS indications	271	19.7
Research	37	2.7
Other indications	221	16.1
Total number of patients treated	1374	100

(The British Hyperbaric Association. Register of Member Chambers 1998).[9]

Table 7 shows hospital admissions in the West Midlands region (population approximately 5.2 million) for 1995/96 for the conditions identified by the HBA and UMHS (where coding was available). There were a total of 2,672 admissions, including over 1,000 cases of severe haemorrhagic anaemia, 916 thermal burns, 354 cases of osteomyelitis and over 100 for

osteoradionecrosis. It is difficult to get accurate data on a number of the other conditions HBO_2 is advocated for, e.g. wound problems, due to coding deficiencies.

Table 7 – Admissions in the West Midlands 1995/6

Condition	Number of Admissions
CO poisoning	157
Gas gangrene	6
Anaemia	1094
Air embolism	10
Osteomyelitis	354
Osteoradionecrosis	131
Thermal burns	916
Crush injury	4
Total	2672

The number of deaths due to non-intentional carbon monoxide poisoning has decreased steadily in England and Wales since the replacement of carbon monoxide rich town gas with natural gas between 1967-1972.[2] However, the number of suicides involving carbon monoxide has increased considerably, more than trebling in number in 16 years.[2] It has been suggested that this could be partly due to the news coverage of such deaths and the popularity of hatchback cars, which require shorter hosepipes. Suicide using car exhaust fumes has been described as the "modern self poisoning method".[16]

A study of mortality and hospital admission data found that over the period January 1988 to December 1994 in the West Midlands, 701 patients were admitted to hospital as a result of carbon monoxide poisoning. In the same period 939 deaths were reported. The linked data set (admissions and deaths) recorded 1633 unique incidents.[2]

There were 30 extra contractual referrals to HBO_2 due to carbon monoxide poisoning from North Staffordshire Health Authority in 1995/96 at a cost of £56k. This represents a rate of 6.7 admissions per 100,000 compared with an expected rate of 0.7 per 100,000.[1] It has not been possible as yet to obtain data from the other twelve health authorities.

Given the range of conditions for which HBO_2 is advocated this review has attempted to focus on those where there is a significant literature and/or those of most importance to the West Midlands. Although there are no clinical trials (or any likelihood of any) on the treatment of decompression sickness and embolism, the principles of physical science substantiate the use of HBO_2 in such cases and these conditions were not included in the review. Carbon monoxide poisoning, anaemia, osteomyelitis, osteoradionecrosis and burns are important in the region in terms of demand (see table 7). On the basis of the initial scoping searches and discussions with key witnesses a sizeable potential literature was identified on these conditions together with gangrene and skin grafts/flaps. Once the study criteria were refined to randomised controlled trials (RCTs), gangrene, osteomyelitis and acute anaemia were withdrawn from the review.

3 Nature of the Key Conditions

3.1 Carbon Monoxide Poisoning

Introduction

The danger of smoke inhalation has been known and described as a toxicological phenomenon since the times of Galen and Hippocrates. Carbon monoxide has been known to be poisonous since the mid-1800s and carbon monoxide poisoning still kills about 1,000 people each year in England and Wales.[1] It is a colourless, odourless, tasteless and non-irritating gas slightly lighter than air.[17] Carbon monoxide is readily absorbed through the alveoli and combines with haemoglobin to form carboxyhaemoglobin (COHb) reducing the total capacity of the blood to carry oxygen. This affinity is 200-250 times that for the formation of oxyhaemoglobin. Carbon monoxide binds tightly to haemoglobin tetramers and this shifts the dissociation curve of any remaining oxyhaemoglobin to the left (the Haldane effect) thus increasing tissue anoxia. 10-15% of the carbon monoxide binds to myoglobin. This affinity is 40 times greater than oxygen and may cause direct myocardial depression.[1] Carbon monoxide toxicity may also be due to inhibition of cellular respiration; carbon monoxide binds reversibly to cytochrome oxidases a3 and P450 and may also inhibit the respiratory function of mitochondria.[18]

3.1.1 Sources

The most important source of ambient carbon monoxide is the petrol engine vehicle and this has become more dominant as traffic has increased. Catalytic converters reduce carbon monoxide emissions significantly but these have only been compulsory in new cars in the UK since 1993.

Some groups may be occupationally exposed, for example traffic police, garage workers and fire fighters. Paint strippers containing methylene chloride may also give rise to exposure as it may be absorbed through the respiratory or gastro-intestinal systems and be metabolised to carbon monoxide.[19]

Poisoning may occur in the home due to poorly maintained and/or fitted gas fired appliances including water heaters, fireplaces and space heaters.[1] Faulty gas appliances cause around 30 deaths each year in England and Wales.[20] Carbon monoxide poisoning may also occur in a variety of enclosed spaces due to inappropriately used machinery or equipment, for example petrol powered pressure washers [21] and travelling in the back of trucks.[22] Reports have been received of cases associated with unswept chimneys in Northern Ireland.[23]

3.1.2 Signs and Symptoms

The brain and heart extract the greatest percentage of oxygen and consequently are affected most significantly and earliest in an exposure. The classic signs of cherry-red lips, cyanosis and retinal haemorrhages are actually, however, relatively rare.[24] Occasionally, severe poisoning will produce areas of erythema, oedema and blistering.[25; 26] Patients may complain of blurred vision or even blindness in extreme cases. Severe exposure (5000 ppm) can be fatal.[17] However, even in the case of an acutely poisoned person, symptoms may be varied, non-specific and are only roughly correlated to COHb levels.[25] Indeed, the circumstances in

which the patient is found, rather than the symptoms displayed, may be the best indication of carbon monoxide poisoning. The severity of poisoning depends on the carbon monoxide concentrations, duration of exposure and health of the exposed person.[27] Infants, the elderly and patients with cardiovascular disease, anaemia, lung disease or increased metabolic rate are at greatest risk.[27; 28]

Carbon monoxide readily crosses the placenta to expose the foetus and foetal COHb levels are 10-15% higher than the mother, with uptake occurring more slowly.[29] Equilibrium takes approximately eight hours in the mother and 36-48 hours in the foetus. While severe carbon monoxide poisoning presents serious foetal risk, mild exposure is not significant.[30] Carbon monoxide appears to have teratogenic and embryotic potential when exposures are sufficient to cause a significant increase in maternal COHb or in cases of moderate to severe maternal toxicity.[31]

3.1.3 Diagnosis and Treatment

Carbon monoxide poisoning is difficult to diagnose as the clinical features are non-specific and mimic common conditions such as unstable angina, drug overdose and epilepsy. The textbook cherry red colour is actually a relatively uncommon finding.[24] In addition, as the gas is colourless, odourless and non-irritant, the patient may be unaware of the exposure or indeed may be affected by impaired consciousness and therefore unable to describe exposure.

When carbon monoxide poisoning is suspected, COHb levels should be determined. The only undisputed response in all cases of carbon monoxide poisoning is the removal of the patient from the source of carbon monoxide. However, it is well documented that oxygen shortens the half-life of carboxyhaemoglobin [32] and the two main treatments are 100% oxygen at atmospheric or hyperbaric pressure. Normal adults breathing air at sea level have an average COHb half-life of 320 minutes. The literature suggests that breathing 100% oxygen reduces the half-life to between 27 and 462 minutes. The half-life is decreased further using HBO_2 but the effect varies considerably in the literature, 23 minutes at three atm abs, 27 minutes at 1.58 atm abs and 15-22 minutes at 2.5 atm abs.[33] It should be remembered, however, that COHb levels are not a reliable indicator of the severity of poisoning and that symptoms can still occur following reoxygenation.

3.2 Osteoradionecrosis

3.2.1 Signs and Symptoms

Osteoradionecrosis (ORN) is the death of previously radiated bone. Patients who have had radiation treatment to their jaws for cancer become predisposed to this condition. Radiation causes bone to become less cellular, less vascular and have less oxygen. The marrow suffers vascular injury leading to sclerosis of the marrow, connective tissue and arteritis of the narrow vessels.[34] This results in a compromised ability of the bone to heal after a traumatic event. Radiation destroys salivary glands and as dental decay is more likely to occur in the absence of active salivary flow, tooth extraction is common in such patients. The removal of a tooth from an irradiated jaw can often result in ORN and the loss of the jaw.

ORN is not a primary infection of irradiated bone but is induced by a metabolic and tissue homeostatic deficiency due to radiation induced cellular injury.[34] In these damaged tissues, macrophages are not stimulated and fibroblasts fail to lay down new collagen leading to chronic non-healing wounds.[35] Conditions that compromise micro-vascularity such as diabetes, periodontal disease and hypertension probably increase the risk of ORN. Although there is a greater risk with higher radiation doses, ORN can occur at relatively low dose levels.[35] Local wound care and good oral hygiene play a major role in the treatment of ORN.

3.2.2 Diagnosis and Treatment

In patients treated with radical radiotherapy for oral or oropharyngeal primary malignancies, the incidence of ORN is around 14%.[35] Surgery is an important element in the management of ORN and may include local debridement, sequestrectomy or resection of large segments of the mandible.[35]

3.3 Thermal Burns

3.3.1 Signs and Symptoms

Burn lesions are essentially a series of zones of injury [36] and can be classified accordingly (table 8):

Table 8 – Burns classification

Superficial burns epidermis only red, pink or erythematous areas dry; rarely blister delayed pain some swelling, particularly if eyes are involved spontaneous healing in three to five days generally no scarring
Superficial partial-thickness burns epidermis and superficial dermis (papillary dermis) large, intact blisters present large amounts of exudate when blisters rupture or are removed extremely painful brisk capillary refill when skin is blanched spontaneous healing in seven to ten days (reepithelialization) minimal scarring (generally pigment alteration)
Deep partial-thickness burns epidermis, papillary dermis, and reticular dermis mix of red and waxy white large amounts of exudate slow, sluggish capillary return when skin is blanched generally dull pain massive swelling; can cause problems with range of motion spontaneous healing in two to three weeks (scar production) hypertrophic scarring and scar contracture likely
Full-thickness burns entire thickness of skin through reticular dermis mosaic of colours possible, including black, tan, red, white no blanching; reddened areas stay red when pressure is applied (hemoglobin from ruptured red blood cells trapped in tissue) thrombosed superficial blood vessels (intense heat causes cell coagulation, blocking blood vessels) poor circulation to distal area of full-thickness injury leathery, rigid, dry tissue swelling below eschar but not in area of eschar; burn area may appear depressed

escharotomy or fasciotomy may be needed to relieve pressure from swelling insensate areas because of nerve destruction body hairs easily slip out of hair follicles healing through skin grafting procedure scarring around periphery of wound or between skin grafts Subdermal burns beneath level of dermis; involve subcutaneous tissue (fat, bone, muscle, tendon) typically result from electrical injury mummified and devitalized appearance thrombosed blood vessels neurologic involvement possible muscle paralysis possible insensate areas little swelling tissue deficits healing through skin graft or flap scarring around periphery of wound or between skin grafts

Adapted from Staley and Richard [37]

Burns always create an injury site that is surrounded by normal tissue which usually includes the skin and subcutaneous tissues but may also involve deeper structures such as blood vessels, muscle and bone. Tissue oedema causes spreading of the cells which together with the decrease in perfusion by the injured blood vessels increases the diffusion distance and decreases the rate of oxygen transfer. This may cause cell damage or even death. Direct cell damage and death may be caused by heat. This may affect the different levels of the epidermis and dermis depending upon severity.

3.3.2 Treatment

Oxygen is required in the healing of all types of burn injuries. The aims of burn wound management are the same as those for any wound: minimise infection by removing necrotic tissue, provide a moist healing environment, minimise scarring and protect the wound from further trauma.[37] Most patients with acute burns will undergo some hydrotherapy. Topical antimicrobial agents may be applied to prevent infection or sepsis and systemic growth hormone has been used in patients with large burns to encourage healing. Dressings will be used to provide a moist environment, debride the wound, absorb exudate and/or prevent infection. Biological dressings such as temporary skin substitutes can also maintain a clean wound. Blisters are often removed as they obscure the view of the underlying wound and may also inhibit white blood cells function.[37]

3.4 Skin Grafts

Skin grafts are layers of skin which are taken from a suitable donor area of a patient and transplanted to a recipient area of damaged skin. Skin grafting is used to replace skin cover, e.g. it is used in the treatment of extensive burn areas of skin, varicose ulcers and after surgical excision of skin cancers including malignant melanomas. A full thickness burn or a wound that takes longer than three weeks to heal will usually be treated with a graft. A split thickness graft is made up of the epidermis and a portion of the underlying dermis. The donor skin can be expanded in a mesh graft to increase the coverage in the case of large burns. Thinner grafts survive transplantation more readily and are more successful. They are used for heavily contaminated surfaces, burn areas and surfaces with a poor blood supply. However, they are least like normal skin with loss of suppleness, hair does not tend to grow on them and their final appearance can be disappointing. They will usually be avoided in cosmetically important areas as a mesh scarring will remain. A full thickness skin graft involves the use of the whole thickness of skin and the graft is stapled or sutured over the wound. These grafts are more robust than the split thickness grafts.[37]

3.5 Crush Injury

3.5.1 Signs and Symptoms

Crush injury is caused by continuous prolonged pressure or shearing forces. After initial removal from the source, there is often severe neurological deficit although no pain. Oedema develops quickly and muscle death and leakage leads to swelling. Compartment injury or syndrome is a particular type of crush injury, which may occur anywhere a muscle is enclosed in a fascial space. The cause is an elevation in pressure resulting in the occlusion of venous drainage, compromise of arterial supply and subsequent muscle necrosis.[38]

3.5.2 Diagnosis and Treatment

Treatment may involve the use of crystalloid to address hypovolaemia, mannitol if there is diuresis and acetozolamide if blood pH is elevated. Surgery may be particularly important as fasciotomy may prevent muscle death.[38]

4 Proposed Service

4.1 HBO_2 Facilities

There are currently no HBO_2 facilities in the region although a HBO unit has been proposed for the City Hospital Trust Birmingham to cover both the emergency and elective HBO_2 work within the West Midlands region. Clinicians make a judgement whether to refer a patient for HBO_2. These include emergencies such as carbon monoxide poisoning and decompression sickness and electives such as post-radiotherapy tissue damage. The absence of facilities in the region may act as a disincentive to referral. It is anticipated that if a HBO_2 facility was provided within the region, it would be used as the primary treatment in severe cases of carbon monoxide (despite the lack of evidence) and be offered for the treatment of other conditions (See tables 1 and 2). Guidance on referral criteria is available from the BHA.[9]

4.2 Range of Conditions

HBO_2 has in the past been recommended for an extraordinary range of conditions (see table 3) yet the only unequivocal consensus for its use is in the treatment of decompression sickness and air embolism. Considerable scepticism over the treatment's value has developed even in cases of severe carbon monoxide poisoning where it has generally become the treatment of choice. The West Midlands will continue to treat its few cases of decompression sickness and air embolism by referral to HBO_2 and will probably continue to refer in cases of severe carbon monoxide poisoning. Some individual consultants will also continue to refer for osteoradionecrosis and similar conditions. There are two questions to address. Firstly, should the West Midlands refer cases of the conditions considered in this review to HBO_2 at all and if so, secondly, is there a case for establishing a facility in the region. The latter depends to a degree upon the balance between the costs versus benefits of using out of region HBO_2 facilities at a 'de minimis' level and the costs versus benefits of a regional facility which would almost certainly allow a greater number of treatments for a greater number of conditions to be carried out.

5 Questions Addressed by the Review

5.1 Statement of Question:

1 Is HBO_2 beneficial in the management of:

a) Carbon monoxide poisoning;
b) Osteoradionecrosis;
c) Thermal burns;
d) Skin grafts/flaps;
e) Crush injury?

2 If yes to any of the above, is there a financial case for a health service HBO facility in the West Midlands?

5.2 Outcomes

Carbon monoxide poisoning	Regaining consciousness, reduction of delayed neurological symptoms, survival.
Osteoradionecrosis	Wound healing, incidence.
Thermal burns	Relief of hypoxia, decrease in fluid losses, limiting burn wound extension and conversion, treatment of oedemas, promotion of wound closure, length of stay.
Skin flaps/grafts	Acceleration of angiogenesis, promotion of healing, graft survival.
Crush injury	Wound healing, major surgery, time of healing, length of stay.

5.3 Previous Reviews

Tibbles and Edelsberg concluded that the discovery of beneficial cellular and biochemical effects of HBO_2 had strengthened the rationale for the treatment in the management of some conditions but considered that the paucity of RCTs made assessment of effectiveness difficult.[7]

Lindell Weaver, in his recent review paper on carbon monoxide poisoning, concluded that the evidence regarding the effect of HBO_2 on the development of cognitive sequelae was inconclusive.[33]

Mitton and Haily's review of HBO_2 concluded there was good evidence of effectiveness for its use in the treatment of severe carbon monoxide poisoning, osteoradionecrosis, diabetic leg ulcers and gas gangrene.[14] The review also concluded that there was no evidence to support HBO_2 in the treatment of osteomyelitis, thermal burns, compromised skin grafts/flaps, acute anaemia or crush injury.

The Wessex Institute of Public Health Medicine reviewed HBO_2 for the treatment of gas gangrene, carbon monoxide poisoning, burns, soft tissue injury and major wound healing and concluded that HBO_2 is expensive and that clinical trials were needed to establish the case.[39] The review identified no RCTs for gas gangrene, considered the role of HBO_2 in carbon monoxide poisoning to be poorly understood and its role in the treatment of burns as not yet entirely justified.

Tibbles and Perrotta found some support for HBO_2 in the treatment of carbon monoxide poisoning although found no RCT demonstrating a clear advantage of HBO over Normobaric Oxygen (NBO).[40] Their review recommended further study.

The University of British Columbia Centre for Health Services and Policy Research reviewed HBO_2 for osteomyelitis and osteoradionecrosis and identified one non-randomised trial for

the former and one RCT for the latter.[41] The review concluded that there was no evidence that HBO_2 was effective in the treatment of osteomyelitis although there may be indications for the treatment of osteoradionecrosis. However, the paucity of literature made any definitive conclusion difficult.

This review builds on and updates the previous work. This is important as there have been some relevant studies published since the earlier reviews. This review also concentrates on the better quality literature (RCTs) and on those conditions of particular concern to the West Midlands region.

6 Methods

6.1 Development of the Protocol

The protocol for this report was developed within the University of Birmingham Development and Evaluation course 1998/99 with the support of the course team. A body of literature held by Dr Giri Rajaratnaram, Director of Public Health, North Staffordshire Health Authority and Mr Gary Ward, Accident and Emergency Consultant, Coventry and Warwick Hospital Trust was used to inform the background to the review, to formulate the question and to refine the final search strategy. The protocol was subjected to the scrutiny of Dr Chris Hyde and Ms Jackie Young of the West Midlands Aggressive Research Facility and appropriate amendments made.

6.2 Literature Search

A broad scoping search strategy was developed to identify any potentially relevant material. The key elements of this strategy included

- Electronic searches of MEDLINE, TOXLINE and BIDS using ‘hyperbaric oxygen’, ‘normobaric oxygen’;
- Searches of the Cochrane Library Controlled Clinical Trials Register;
- Contact with experts in the field (see appendix 1);
- Citation checking.

All sources were searched from 1968 onwards. No language exclusion or study design limits were applied.

6.3 Criteria for Including Studies

The inclusion and exclusion criteria were made independently of the detailed examination of the studies and were applied using predetermined criteria.

Data were abstracted from the included studies by one reviewer using a predetermined form (Appendix 2). Microsoft Access and Reference Manager were used to manage the data.

Randomised Controlled Trials were included. Inclusion criteria were as follows:

Population:

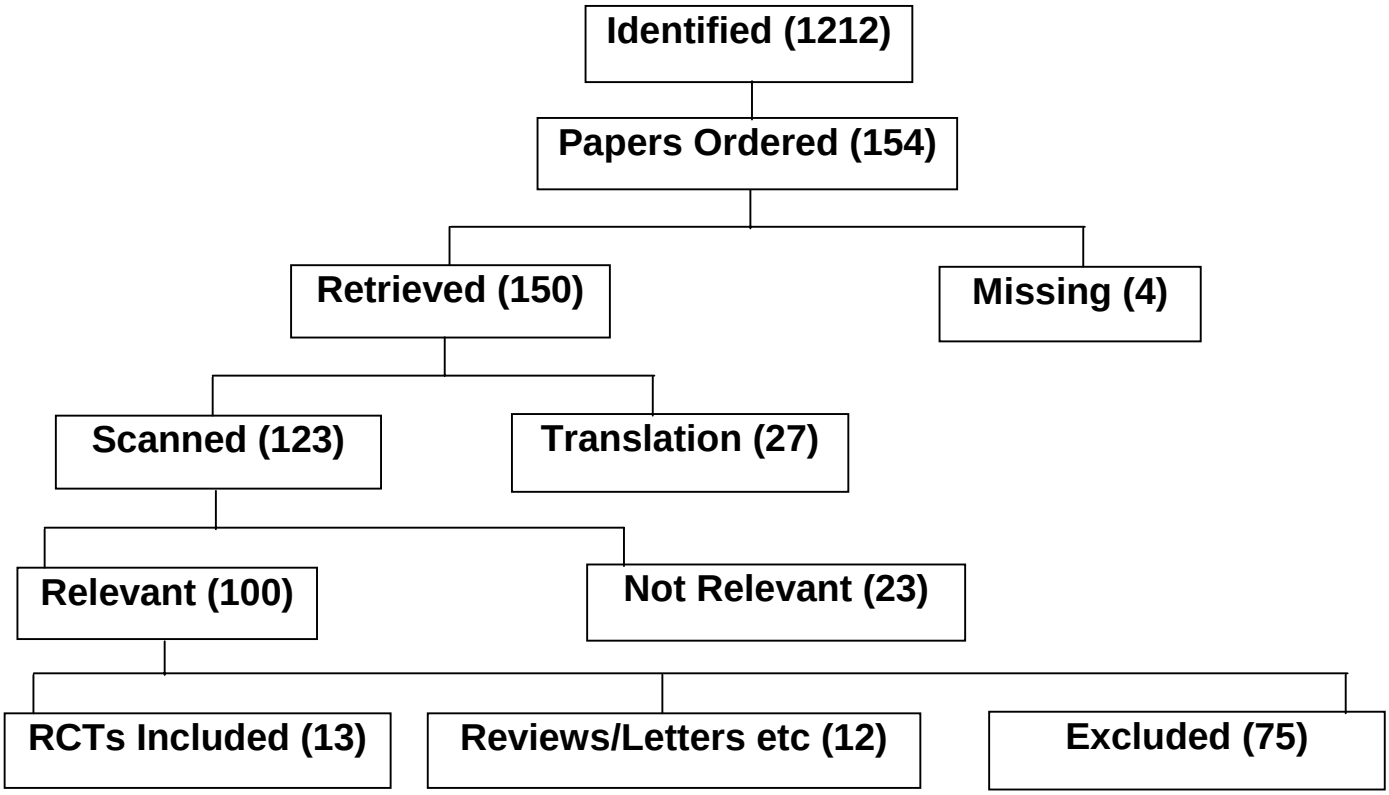
Patients with either:
Carbon monoxide poisoning, osteoradionecrosis, thermal burns, skin grafts/flaps or crush injury.

Intervention:

Hyperbaric Oxygen Therapy.

Figure 4 shows the breakdown of papers retrieved

Figure 4 - Research Papers



6.4 Search Strategy

The search strategy is given in Appendix 3.

The following databases were searched:

Electronic databases:

Medline
Embase
BIDS
Toxline
HSE line
Cochrane
Health Star
HTA
Current awareness in Clinical Toxicology

Internet:

The main search engines were used using the term hyperbaric oxygen.

Handsearching:

Reference lists were examined for further references and contact made with experts in the field (Appendix 1). The personal files of Drs Bryson, Ward and Rajaratanam were searched.

7 Evidence of Effectiveness

7.1 Volume of relevant material

Initially 1212 references were identified by formal search. 154 full text papers were obtained where they were potentially relevant for inclusion or the title and abstract contained insufficient information on which to base a decision. 150 of these papers were retrieved and 27 referred to translation (this review has been completed without the foreign language papers). 13 relevant RCTs and 12 reviews were identified. The main reason for exclusion was inappropriate study design. Details of all included studies are given in Appendix 4.

7.2 Overall characteristics of studies identified

A total of 13 RCTs were identified, four completed trials and the published interim results of another two trials on carbon monoxide poisoning, two on osteoradionecrosis, three on thermal burns and one each for skin grafting/flaps and crush injury. The volume of relevant literature, with the exception of carbon monoxide poisoning, is clearly very light. An additional problem was the lack of consistency with treatment protocols, study populations,

exposure and outcome measures all differing from study to study. Several studies had very small numbers (26 and 12 in two studies) and only six were blinded.

7.3 Carbon Monoxide Poisoning

Four completed published RCTs and the published interim results of another two studies were identified [42; 43; 44; 45; 46; 47](See table 9 and Appendix 4 for characteristics). While all these trials were randomised and prospective, blinding was variable. Only two trials were double blind[45; 47], three were non-blinded [42; 44; 46] and in one case it is not clear whether blinding occurred.[43] The only core inclusion criterion was carbon monoxide poisoning but even this varied in degree from moderate to severe. There were no core exclusion criteria defined. Treatment and comparator protocols varied from study to study, HBO_2 ranging from 2.0 atm abs to 2.8 atm abs and duration from 90 minutes to two hours. A range of outcomes were assessed (often poorly defined). Neuropsychiatric outcomes were most commonly measured although there were no common testing protocols. Numbers enrolled in the studies varied (where given) from 26 [42] to 629.[44] The time to treatment varied from <1 hour to 27 hours.

Of the six studies, three reported a beneficial effect of HBO in terms of delayed neurological symptoms (DNS) [42; 43; 46] (one in acutely poisoned [46], two in moderately poisoned patients [42; 43]). Two of these studies were non blinded [42; 46] and it is not clear whether the third was blinded or not.[43] One study only recruited 26 patients.[42] Two studies reported no effect of HBO_2 [44; 47] (one double blinded study of acutely poisoned patients [47], one non-blinded study in both acutely and moderately poisoned [44]) and one double blinded study found an adverse effect of HBO_2.[45] These studies enrolled relatively large numbers of patients (152, 196, 629). The best quality studies found no beneficial effect of HBO on DNS.

7.3.1 Carbon Monoxide Poisoning (details of included studies)

Raphael et al attempted to test whether conscious carbon monoxide poisoned patients would benefit from HBO_2 and whether unconscious patients would benefit from two sessions of HBO_2 compared to one in an RCT over almost four years from November 1983.[44] Patients over 15 years of age admitted to hospital within 12 hours from the end of an accidental exposure at home and whose poisoning was confirmed by COHb level exceeding 10% or above 5% for smokers and non-smokers respectively were included. 343 patients with no initial loss of consciousness were randomised to a treatment arm (two hours HBO at two atm abs plus four hours NBO, n = 173) and a control arm (six hours NBO, n = 170) and the percentage of patients recovering after one month using self assessment questionnaire and examination compared. There were no significant differences in the recovery rate even when all those lost to follow-up (n = 70) were assumed to have recovered. To test the effect of two HBO_2 sessions, 286 patients with initial loss of consciousness were randomised to receive one or two sessions of HBO. Again no differences in recovery rate were identified. However, in both studies assessing symptoms at one month may miss a beneficial effect of a more rapid recovery in treated patients and the level of HBO_2 is lower than that given in most studies in this area. This study was not blinded and while the time to randomisation was generally less than six hours, the time to treatment was anything up to 12 hours from the end of exposure. A number of studies have indicated that early treatment is important.[39; 42; 46] The absence of a standardised cognition test may also have made detection of subtle changes difficult.

Table 9 – Characteristics of Included Studies: Carbon Monoxide

Study ID(Location)	Results	Comments	Ref (Date)
155(Australia)	HBOT group significantly worse outcome on completion of treatment: number of abnormal tests, learning test. Significantly more severely poisoned patients in the HBOT group with poor outcome.	Study shows that HBOT had a detrimental effect. Double blinded.	Scheinkestel et al 1999 [45] (9/93 – 12/95)
152(France)	Significantly fewer symptoms in HBO group at three months ($p < 0.016$)	Interim analysis. No evidence of blinding.	Mattieu et al 1996[43]
154(US)	No difference in interim analysis after 50 or 100 patients	Study completed but analysis ongoing. 152 patients enrolled. Double blinded.	Weaver et al 1995 [47]
24(France)	Significantly more HBO treated patients normal at two hours ($p<0.01$) and12 hours ($p < 0.05$)Significantly better EEG results in HBO group at 21 one days ($p < 0.02$)	Indicates that early treatment with HBO prevents delayed effects. However, patients had no clinical sign of delayed syndrome. 25 patients received oxygen during transit to hospital and no data provided on the distribution of these, no details of the sub set subject to EEG at 21 days and study was not blinded. Small numbers	Ducasse et al 1995 [42]
36(US)	Significantly more NBO patients developed DNS ($p < 0.05$).	Not blinded, five patients lost to follow up and only eight people used to form the control group to test the effect of familiarity with testing.	Thom et al 1995 [46] (9/89 – 12/93)
33(France)	No significant differences in recovery rate.	Not blinded, 70 patients lost to follow up. Up to 12 hours between poisoning and treatment.	Raphael et al 1989 [44] (11/87-9/87)

Thom et al [46] conducted an RCT during 1989 - 1993 to test whether the incidence of DNS would be affected by HBO_2. 65 patients with a history of acute carbon monoxide poisoning, elevated levels of COHb or presence of symptoms consistent with carbon monoxide exposure were randomised to a treatment group (2.8 atm abs for 30 minutes, two atm abs for 90 minutes, n = 33) or comparison group (NBOT until symptoms resolved, n = 32). HBO_2 was started within six hours of removal from carbon monoxide source. Patients were subjected to a neuropsychological screening battery within 12 hours of treatment and four weeks after treatment. An additional control group (n = 8) was also tested to identify any effect on scores of repeated testing. While there were no significant differences in the neurological status of the two groups immediately following treatment, the NBOT group developed more DNS symptoms *($p < 0.05$)*. However, this was a non-blinded study and five patients were lost to follow-up. In addition, only eight people were included in the control group to test the effect of familiarity with testing.

Ducasse et al [42] compared the effects of NBO and HBO on moderate carbon monoxide poisoning in an RCT published in 1995. A total of 26 non-comatose patients who had suffered acute carbon monoxide exposure for less than 12 hours and who were hospitalised within two hours of discovery were randomised to HBO_2 (2.5 atm abs for two hours, 100% NBO for four hours followed by 50% NBO for six hours, n = 13) or to NBOT (six hours at 100%, six hours at 50%). The mean time from exposure to treatment was 53 minutes (no range given) and patients were examined on admission and at two hours and 12 hours. Electroencephalograms (EEGs) were performed within 24 hours and approximately three weeks after poisoning. Cerebral blood flow was measured in a subset of ten patients (four HBO_2, six NBOT)

The HBO_2 group showed significant improvement at two hours in terms of resolution of symptoms and in EEG recordings in a subset after 21 days. However, there was no significant difference between the groups in the 26 EEG readings obtained from all the included patients within the first 24 hours and all patients were ultimately discharged without abnormal clinical findings. There was a cerebrovascular hyperactivity in the NBOT group of the subset. This study indicates that early treatment with HBO_2 leads to earlier resolution of some symptoms. It is not clear whether there was a small number of patients with multiple abnormalities or a larger number of individuals with fewer abnormalities in the NBOT group. In any case, there was only a total of five abnormalities at 12 hours. While the patients were exposed for less than 12 hours there is no indication of the range of exposures or distribution between the treatment and control groups. 25 patients received oxygen during transport to the hospital but again there is no indication as to their distribution. The study was unblinded, involved small numbers and no details of the subgroup were given.

Mathieu et al [43] reported the interim results of an RCT comparing the effect of HBO with NBO in non-comatose carbon monoxide poisoned patients. 575 non-comatose patients admitted with COHb >10% within 12 hours of poisoning were randomised over three years to HBO (2.5 atm abs for 90 minutes, n = 299) or 12 hours of NBO (n = 276). Persistent neurological symptoms were assessed at one month, three months and 12 months. There were no significant differences at one month or 12 months although at three months 9.5% of HBO patients had symptoms compared with 15% of NBO patients *($p = 0.016$)*. No details of the neurological testing, time taken to treatment or method of blinding (if used) were given.

In a double blinded RCT, Scheinkestel et al [45] randomised 191 patients to HBO (100 minutes 100% oxygen including 60 minutes at 2.8 atm abs, n=104) or NBO (100% oxygen at 1.0 atm abs for 100 minutes, n = 87). The chamber was flushed regularly with air to simulate pressurisation in the NBO group. All patients received three treatments once a day and underwent full neuropsychological assessment after the third treatment and at one month. Time to treatment was 7.5 hours (6.6 –8.6) for the HBO group and 6.6 hours (5.7 – 7.5) for the NBO group. There were no significant differences in age, sex or baseline severity between the groups. Testing was conducted by a clinical psychologist using computerised testing.

A smaller proportion of NBO patients were considered to be medically or neuropsychologically impaired after three treatments. The only significant result revealed that the HBO group performed less well than the NBO group in the learning test at completion of treatment in all patients (*p=0.01*) and severely poisoned patients (*p=0.005*). NBO patients had significantly fewer abnormal test results at completion of treatment (*p=0.02* for all patients and p=0.008 for severely poisoned). There were five cases of delayed neurological symptoms; all in the HBO group. Analysis of patients beginning treatment within four hours showed no difference in outcome.

Criticisms of this study include the use of cluster randomisation, the lack of baseline neuropsychological assessments, the intensive NBO and HBO regimes, the follow up rate and the lack of information on numbers of severely affected patients with long delays to treatment.[33] It is also unclear whether the patients were actually unaware of the treatment allocation.[3]

In their review of HBO_2 and carbon monoxide poisoning Tibbles and Perrotta [40] considered that while there was some support for HBO_2 in the treatment of carbon monoxide poisoning, there is a need for a well designed, multicentre prospective study. Weaver has written compellingly on the need for such an RCT to provide sound evidence to underpin the use of HBO_2 for acutely poisoned persons.[33; 48] Weaver and colleagues have recently completed such a study involving 152 patients although the analysis is incomplete to date. This double-blinded RCT included acutely poisoned patients with analysis stratified by age, time from exposure to randomisation and loss of consciousness. Neuropsychological testing was administered following the first and third treatments, at two and six weeks. While definitive conclusions cannot be drawn at this stage, interim analysis at 50 and 100 patients and initial analysis at 152 patients has indicated no outcome differences between the HBO and NBO group.[47]

7.4 Osteoradionecrosis

7.4.1 Studies identified

Two RCTs were identified [49; 50] (see table 10 and Appendix 4). One was double blinded although only recruited 12 patients [50], the other non blinded.[49] The former dealt with healing in cases of osteoradionecrosis, the latter with the prevention of osteoradionecrosis in high risk patients.

The treatment and comparator protocols differed and patient characteristics were not given in either paper. Time to treatment was not defined. The double blind study reported significant

improvement in healing in the HBO_2 group compared to NBOT group although was cautious about the validity of the results. The other study found a significantly lower occurrence of osteoradionecrosis in a group of high risk patients treated with HBO_2 compared to a group treated with penicillin.

7.4.2 Details of included studies

Tobey and Kelly [50] describe a double blind RCT to test whether HBO_2 at two atm abs was more effective than 100% oxygen at 1.0 atm abs in the treatment of osteoradionecrosis of the mandible. 12 patients were treated two hours a day, five days a week for eight weeks. They reported significant improvement in healing in the HBO_2 group. However, this study involves small numbers, gives two different atm abs values for the control group (1 and 1.2), does not provide any details of the patients in each group and the authors state that the observations could not, at that time, be validated.

Marx and Johnson [49] conducted a RCT comparing HBO_2 with penicillin in the prevention of osteoradionecrosis after tooth removal in a high risk patient population. 74 patients with indication of removal of one or more teeth in a segment of the mandible that had received >6000 rads were randomised to a treatment group (2.4 atm abs for 90 minutes. 20 sessions prior to, and ten sessions post, tooth removal. Sessions conducted once daily for five or six days a week, n = 37) and comparison group (penicillin treatment, n = 37). There was a significant reduction in the rate of osteoradionecrosis in the HBO_2 group. This study was not blinded and provided no background data on the two groups other than numbers.

7.5 Burns

7.5.1 Studies identified

Three RCTs were identified [51; 52; 53] (see table 11 and Appendix 4). Two were blinded [52; 53] with one of these an experimental design involving the creation of standard burn wounds on a small group of volunteers.[53] In the other two, patients were treated within 24 hours [51; 52] but only one specified the degree of burn.[52] Treatment and comparator protocols differed. Outcomes varied although healing time was common to two. Time to treatment varied from two to 24 hours. The two blinded studies involving small numbers (16 and 12) [52; 53] found a significant effect on healing time although the difference was short-term in one study.[53] The larger, albeit non blinded, study found no effect of HBO_2.[51]

Table 10 - Characteristics of Included Studies: Osteoradionecrosis

Study ID(Location)	Results	Comments	Ref (Date)
73(US)	Significant reduction in rate of osteoradionecrosis in HBOT group.	Not blinded. No data on the two groups provided. Does not define time to treatment.	Marx et al (1985)[49]
14(US)	Significant improvement in HBOT group.	Paper gives two different values for comparator (1 or 1.2 atm abs). Very small numbers. No details of distribution or characteristics of patients. Blinded.	Tobey & Kelly (1979) [50]

Table 11 - Characteristics of Included Studies: Burns

Study ID(Location)	Results	Comments	(Ref Date)
22(US)	No difference in LOS, mortality or number of surgeries between the two groups.	Not blinded	Brannen et al (1997)[51]
30(US)	Significant reductions in hyperaemia in HBO group on day two ($p<0.05$), wound size ($p<0.03$) and exudation ($p<0.04$)	Small numbers although blinded. Hyperaemia same by day four, wound size by day three and no evidence that exudation reduced to zero any faster in HBO group.	Niezgoda et al (1997)[53]
13(US)	Significant reduction in healing time $p<0.005$.	Small numbers although blinded. Distribution of males and females not given.	Hart et al 1974 [52] (11/72-1/74)

7.5.2 Details of included studies

Hart et al [52] conducted an RCT involving 16 patients to examine the effect of HBO_2 on the treatment of serious burns. Patients with thermal burns over 10 to 50% of body surface occurring within 24 hours of injury were randomised into four groups of two pairs stratified by degree of burn. The treatment arm received oxygen at two atm abs for 90 minutes every eight hours for the first 24 hours and then every 12 hours until treated. The control arm received a rapid compression to five lbs/$in^{2,}$ which was then allowed to drift creating the impression of HBO_2. There was a significant reduction in healing time in the HBO_2 group. However this study involved very small numbers and while there was a total of 14 males and two females no details of the age and sex breakdown were given by group. The paper also reports a second study, which compared predicted mortality in 138 patients with HBO_2 and 53 without HBO_2. The HBO_2 group had a mortality rate 30-40% less than predicted. However, the non-HBO_2 group also had a less than expected rate (9% less) and there was no attempt to randomise or match controls.

Brannen et al [51] conducted a non blinded RCT of HBO_2 in the treatment of acutely burned patients admitted within 24 hours of injury. 125 patients were randomised to receive two atm abs for 90 minutes twice daily for a minimum of ten treatments and maximum of one treatment per percentage of total body surface area burn (n = 63). As true randomisation was not available due to the variable availability of the chamber, controls were matched for age, burn size and inhalation injury. Length of stay (LOS) correlated most strongly with number of surgeries, age, area of burn and inhalation injury. No other variable was significant. There was no difference in LOS, mortality or number of surgeries between the HBO_2 and control groups.

Niezgoda et al [53] created standard burn wounds using suction and irradiation on 12 human volunteers and examined the effect of HBO_2 on healing. Patients were randomised to a treatment arm (2.4 atm abs twice daily for three days) or to a placebo arm (8.75% O_2 at 2.4 atm abs) within two hours of the wound being created. Improvements in hyperaemia, wound size and exudation measurements were noted in the HBO_2 group particularly on day two. However, hyperaemia was the same in both groups by day four, wound size by day three and there was no evidence that exudation reduced to zero any faster using HBO_2.

7.6 Skin Grafts

7.6.1 Studies identified

Perrins [54] entered 48 patients presenting for split skin grafting into an RCT and examined the survival of skin grafts in a group treated with 2.0 atm abs for two hours on the evening of the operation and twice daily for three days (n = 24) and a control group (n = 24). He found an improved survival of grafts in the HBO_2 group. However the paper gives no details of the two groups despite patients being accepted regardless of age, sex, graft type or cause of lesion. In addition, the patients were not blinded and it is not clear whether those assessing the outcome were blinded (see table 12 and Appendix 4).

7.7 Crush Injury

7.7.1 Studies identified

Bouachour et al [55] examined the role of HBO_2 in the healing of soft tissue in patients with crush injury in a double blind RCT. Randomising 36 patients with a defined severe limb injury to treatment (2.5 atm abs for 90 minute sessions twice daily for six days, n = 18) or placebo (1.1 atm abs, n = 18) within 24 hours of surgery, a significant effect on wound healing in the HBO_2 group as measured by complete healing or the need for repetitive or new surgical procedures was found. When the patients were matched for age and severity of injury, there was a significant improvement in the management of severe crush injuries in patients over 40 years old. This is the main recommendation of the paper yet the results seem to show a major effect on general wound healing. (See table 12). Curiously the same study is reported by Cronier in 1997 but without reference to the effect on the management of severe injury in patients over 40 years old.[56]

Table 12 - Characteristics of Included Studies: Skin Grafts; Crush Injury

Study ID (Location)	Results	Comments	Ref (Date)
1 (France)	Significant effect on soft tissue wound healing in crush injury patients treated with HBOT particularly in over forty year olds.	Single blinded. No details of patients in both groups.	Bouchour et al (1996)[55]
32 (UK)	Improved survival of skin grafts in HBOT group.	Sex differences between group not defined. Blinded	Perrins DJD (1967)[54]

8 Summary of Evidence

This review has concentrated on HBO_2 in the treatment of carbon monoxide poisoning, osteoradionecrosis, thermal burns, skin flaps/grafts and crush injury. These conditions were selected on the basis of a sizeable literature and/or significance to the West Midlands region in terms of demand. The review has focused on RCTs and identified a total of 13.

One of the difficulties in reviewing the literature is the lack of consistency in the studies. Treatment protocols vary considerably not simply between treatment for different conditions but between treatments for the same condition. The study groups differ in terms of condition, exposure, time to treatment and other characteristics and outcomes measured differ from study to study.

Four completed published RCTs [42; 44-46] and the published interim results of another two trials [43; 47] were identified dealing with carbon monoxide poisoning. There is no compelling evidence that HBO_2 is of benefit in the management of either moderately or severely poisoned patients. The better quality studies conducted on acutely poisoned patients show no effect. However the full results of the Weaver study remain to be published and this should provide valuable additional evidence.[47] This evidence is particularly important as West Midland cases may have to travel considerable distances to receive treatment (see figure 3). This carries its own risks and obviously extends the time to treatment acknowledged as potentially important.

In the case of carbon monoxide poisoning the evidence does not support the provision of an HBO_2 unit in the region and is not convincing enough to warrant the referral of acutely poisoned patients to units outside the region particularly given the potential travel times.

Two RCTs on osteoradionecrosis were identified.[49; 50] One essentially reported an interim analysis and conceded that the observations of an apparently beneficial effect of HBO_2 could not be validated.[50] This review has not found any subsequent publication of the data. The other (unblinded) study demonstrated a significant reduction in the rate of osteoradionecrosis in the HBO_2 group.[49] Again, there is inadequate evidence to substantiate the use of HBO_2 in the treatment of osteoradionecrosis although potential value in further research.

Three RCTs on burns were identified.[51; 52; 53] One blinded study involving small numbers reported a significant reduction in healing time in the HBO_2 group [52] while another much larger non-blinded study reported no effect.[51] A small study involving the creation of standardised burn wounds on volunteers found a short term benefit in hyperaemia, wound size and exudation.[53] Again there is insufficient evidence to substantiate the use of HBO_2 in the treatment of thermal burns.

One RCT on skin grafts and flaps was identified.[54] In patients with major soft-tissue surgery this study found significant improvements in wound dehiscence, infection and healing time in the HBO_2 group. It is not clear whether this study was blinded or not. While there is insufficient evidence to justify HBO_2 in such cases, this appears to be an appropriate area for more research.

One good quality RCT on crush injury was identified which reported a significant effect on wound healing particularly in patients over 40 years old.[55] While this study demonstrated potential, it is insufficient on its own to substantiate HBO_2 as a treatment in such cases.

9 Cost

9.1 Charges for treatment

Charges for treatment vary from unit to unit. This is due in part to the different levels of support required for emergency admissions (such as acute carbon monoxide poisoning) and elective admissions and the different nature of the service providers (some are not for profit) . The cost of an emergency treatment is approximately £150 and for an elective case £250. The cost of treating a severely poisoned person could vary from £6K to £18K depending on severity and number of treatments. Intensive care beds cost in the region of £1,200 per night and a general ward bed may cost £250 per night.[57] Treating burns three times daily for the first 24 hours and then twice daily for 21 days would cost around £12,000 per case, although this could be significantly cheaper in a 'not for profit' unit. The Canadian Centre for Health Services and Policy Research estimates the range of costs of HBO_2 for the treatment of osteomyelitis as between $10,000 - $12,500 or about 5% of overall management costs.[41]

9.2 Cost of HBO units

The cost of HBO units varies from $75,000 - $85,000 (US) for a monoplace chamber and from $300,000 to $2.5 million (US) for a multiplace chamber.[14] A multiplace needs between 1,000ft^2 to 4,500 ft^2 and maintenance costs were estimated to be $5,000/year per monoplace chamber.[14] Staffing costs represent approximately 50% of total operating costs for the larger chambers (approx. $350,000 US).[14]

10 Implications and Conclusions of the Review

HBO_2 has been described as a "therapy in search of diseases" [58] and remains a controversial treatment despite many years of use and research. HBO_2 has been used for an astonishing range of conditions (see table 3) and continues to be used even where research has shown it to be ineffective.[4] The principles of physical science substantiate HBO_2 in the treatment of decompression sickness and air gas embolism despite the lack of any RCTs. However, there is no entirely convincing body of evidence underpinning the therapy in the treatment of other conditions. Conventional wisdom also considers it to be the treatment of choice for acute carbon monoxide poisoning and regards denial of treatment as therefore unethical. Indeed, even those who question its effectiveness feel obliged to recommend it due to medico-legal concerns.[58]

There are no HBO_2 facilities in the West Midlands region and there has been considerable interest in the clinical and financial case for such a unit particularly after an unusually large number of cases of acute carbon monoxide poisoning that had been referred for HBO_2 from one Health Authority in 1995/96.[1]

Twenty-seven foreign languages papers were identified which should now be included in the review. It also became apparent during this review that there is some good quality literature dealing with the impact of HBO_2 on gas gangrene and wound healing although no RCTs for

the former. While HBO_2 is the appropriate treatment for gas embolism and decompression sickness, there is no convincing evidence that it is of benefit for the treatment of carbon monoxide poisoning (severe or moderate), osteoradionecrosis, burns, skin grafts or crush injury. However there is a physiological case for an effect of HBO_2 in conditions involving hypoxia such as osteoradionecrosis and wound healing. This, however, is a national research question rather than a regional issue. An extension of this review to include all controlled trials and wound healing would be warranted.

This review has found no valid case for developing a HBO_2 facility in the West Midlands.

Appendix 1

Key Witnesses

Dr Phil Bryson
Medical Director
Diving Disease Research Centre
Plymouth

Professor Matthew Cooke
The Editor
Pre-Hospital Immediate Care
BMA House
London

Dr Chris Hyde
Director of Aggressive Research Intelligence Facility
Public Health Building
University of Birmingham
Edgbaston, Birmingham

Dr G Rajaratnam
Director of Public Health
North Staffordshire Health Authority
West Midlands

Dr P M Tibbles
Department of Emergency Medicine
Rapid City Regional Hospital
South Dekota

Dr Allister Vale
Director
West Midlands Poisons Unit
City Hospital NHS Trust
Birmingham

Dr Gary Ward
Accident & Emergency Consultant
Coventry & Warwick Hospital
West Midlands

Dr Lindell Weaver
Department of Medicine
LDS Hospital
University of Utah School of Medicine
Salt Lake City

Appendix 2

Data Extraction Sheet

1. Author(s)

2. Centre

3. Title

4. Journal reference

5. Date

6. Ref. No

7. RCT

8. If yes, method of randomisation

9. Research Question

10. Blinded

11. Treatment

12. Comparator

13. Type of Patient/Control – Including Inclusion Criteria

14. Exclusions

15. No. Patients	16. No. Treated	17. No. Controls

18. Loss to follow up

19. Length of Trial

20. Time from exposure to treatment

21. Outcome Measure(s)

22. Results

23. Statistical Tests

24. Comments

Appendix 3

Search Strategy

1. Hyperbaric oxygenation/ or hyperbaric oxygen$.ti,ab,rw,sh.

2. hbo.ti,ab,rw,sh.

3 1 or 2

4 normobaric oxygen$.ti,ab,rw,sh.

5 nbo.ti,ab,rw,sh.

6 4 or 5.

7 3 or 6

8 Carbon monoxide/ or carbon monoxide.ti,ab,rw,sh.

9 7 and 8.

10 Embolism/ or embolism, air/ or pulmonary embolism/ or embolism$.ti,ab,rw,sh.

11 Decompression sickness/ or decompression sickness.ti,ab,rw,sh.

12 10 or 11.

13 7 and 12

14. Fournier's gangrene/ or gangrene/ or gas gangrene/ or gangrene.ti,ab,rw,sh.

15 7 and 14

16 skin flap$.ti,ab,rw,sh.

17 skin graft$.ti,ab,rw,sh.

18 16 or 17

19 7 and 18

20 Burns/ or burns, chemical/ or burns, electric/ or burns, inhalation/ or burn$.ti,ab,rw,sh.

21 7 and 20.

22 Anemia/ or an?emia.ti,ab,rw,sh.

23 7 and 22.

24 Osteomyelitis/ or osteomyelitis.ti,ab,rw,sh.

25 7 and 24.

26 Osteoradionecrosis/ or osteoradionecrosis.ti,ab,rw,sh.

27 7 and 26.

28. Crush syndrome/ or soft tissue injuries/ or wounds, nonpenetrating/ or regeneration/ or muscle, skeletal/or crush injury.ti,ab,rw,sh.

29. Compartment syndromes/ or compartment syndrome.ti,ab,rw,sh.

30 28 or 29.

31 7 and 30.

32 limit 9 to randomized controlled trial.

33 limit 13 to randomized controlled trial.

34 limit 15 to randomized controlled trial.

35 limit 19 to randomized controlled trial.

36 limit 21 to randomized controlled trial.

37 limit 23 to randomized controlled trial.

38 limit 25 to randomized controlled trial

39 limit 27 to randomized controlled trial.

40 limit 31 to randomized controlled trial.

Appendix 4

Details of Included Studies

Carbon Monoxide

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	Ref (Date)
155 (Australia)	Effect of HBO on acutely carbon monoxide poisoned patients.	All patients presenting with significant carbon monoxide poisoning. No data presented other than total number (73).Exclusions: major burns, pregnant women, consent refused.	HBO for 100 minutes. (60 minutes at 2.8 atm abs). NBO 100%, duration not defined.	104 87	22 signs and symptoms. Neuropsychiatric testing after three treatments and at one month.	Scheinkestel et al 1999[45] (9/93 – 12/95)
152 (France)	Comparison of the effect of HBO with 12 hours NBO in conscious carbon monoxide poisoned patients.	Non comatose patients admitted with COHb >10% within 12 hours of poisoning. No data presented except total numbers.	HBO 2.5 atm abs for ninety minutes. NBO 100% for 12 hours.	299 276	Neurological symptoms – not defined. Tests at one, three, six, 12 months.	Mattieu et al1996 [43]
24 (France)	Compare the effects of NBO and HBO on acute carbon monoxide poisoning	Admissions following acute exposure to carbon monoxide for <12 hours. Glasgow coma score >12. Time between discovery and hospitalisation <2 hours. Mean age HBO –28.3 (13.6)NBO – 31.6 (14.1)Mean time from exposure to treatment = 53 minutes. Exclusions: Pregnant women.	100% HBO 2 hours 2 atm abs, 100% NBO 4 hours, 50% NBO 6 hours, 100%NBO 6 hours, 50% NBO 6 hours.	13 13	1.T = 0, Clinical examination at admission. COHb, chest radiography and electrocardiogram.T = 2, Second clinical examination and COHb.T = 12, Third clinical examination COHb, chest X-ray, ECG. within 24 hours of admission and c. three weeks after poisoning.	Ducasse et al 1995 [42]

Carbon Monoxide

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	Ref (Date)
					2.Cerebral blood flow assessed in 4 HBO, 6 NBO and ten normal volunteers.	
36 (US)	Effect of HBO on incidence of delayed neurological syndromes (DNS) in carbon monoxide poisoned patients.	Admissions with history of acute carbon monoxide exposure, elevated COHb or presence of symptoms consistent with carbon monoxide poisoning HBO NBO Age 39 (±3.4) 35 (±2.9) HBO started within 6 hours of removal from carbon monoxide source	HBO 2.8 atm abs for 30 minutes. 2.0 atm abs for 90 minutes. NBO 100% until symptoms resolved.	33 32	DNS. Baseline established within 12 hours of treatment. Symptomatic patients tested on reporting of symptoms and asymptomatic patients within four weeks.	Thom et al 1995(9/89 – 12/93)[46]
154 (US)	Effect of HBO on the incidence of DNS in acutely poisoned patients.	Patients with acute carbon monoxide poisoning >15 years, clinical evidence of poisoning, less than 23 hours from discovery to randomisation.	3 HBO sessions. NBO plus 2 sham HBO sessions	Total 152	Neuropsychological symptoms after first and third treatment, two and six weeks.	Weaver et al1995 [47]

Carbon Monoxide

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	Ref (Date)
33 (France)	Effects of HBO and NBO on unconscious carbon monoxide poisoned patients and the effect of two sessions of HBO in unconscious carbon monoxide patients.	Patients >15 years old admitted to hospital within twelve hours of accidental carbon monoxide poisoning. COHb> 10% or 5% for smokers and non smokers respectively. Two groups – conscious (A) and unconscious (B)Mean age (S.D.) AO,35.6 (14.2); A1,35.2 (13.8); B1,37.8(18.5); B2,37(17.3).	six hours NBO (AO). HBO two hours (30 minutes decompression, 60 minutes 2atm abs, 30 minutes decompression) and four hours NBO (A1 B1) Four hours NBO and two sessions HBO two-12 hours apart (B2).	170 173 145 141	% patients recovered one month after poisoning. Self assessment questionnaire and physical examination	Raphael et al 1989 [44] (11/87- 9/87)

Osteoradionecrosis

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	Ref (Date)
73 (US)	Effect of HBOT in prevention of osteoradionecrosis after tooth removal in high risk population.	Patients with indications for removal of one or more teeth in a segment of the mandible that had received >6000 Rads. Exclusions: Systemic disease such as diabetes, irradiation treatment, <6 months >15 years ago, known contradictions, persistent tumour	HBO 2.4 atm abs for 90 minutes. 20 sessions prior, and ten post tooth removal – one session daily for five-six days a week. Conventional antibiotic treatment.	37 37	Clinical diagnosis	Marx et al1985 [49]
14 (US)	Effect of HBOT on treatment of osteoradionecrosis	Not specified	HBO two atm abs for two hours per day, five days per week for eight weeks. Comparator as above but 1.2 atm abs (or 1.0 atm abs)	Total 12	X-ray interpretation. Clinical signs and symptoms. Soft tissue lesions.	Tobey & Kelly1979 [50]

Burns

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	(Ref Date)
22 (US)	Effect of HBOT in treatment of acutely burned patients.	Acutely burned admitted within 24 hours of injury. Time to treatment – within 24 hours.	HBO 2 atm abs for 90 minutes twice daily for minimum of ten treatments and maximum of one treatment per % total body surface area. Conventional treatment.	63 62	Length of stay. Number of surgeries, mortality.	Brannen et al 1997 [51]
30 (US)	Effect of HBOT on healing of burn wounds.	Volunteers – wounds created using suction and irradiation. Treatment within two hours.	HBO 2.4 atm abs, twice daily for three days. Control 8-7.5% O_2 at 2.4 atm abs.	6 6	Wound size, hyperaemia, exudation	Niezgoda et al 1997 [53]
13 (US)	Effect of HBOT on burn wound healing.	Patients with thermal burns over 10-15% body surface occurring within twenty four hours of such an injury. Mean age HBO = 21.62, Control = 21.31. Exclusion criteria-untreated neoplasm, profound claustrophobia. Time to treatment within 24 hours.	HBO 2 atm abs 90 minutes every eight hours for 24 hours and then every 12 hours until treated. Compressed rapidly to 5lb/in2 and then allowed to drift.	8 8	Healing time, predicted mortality.	Hart et al 1974 [52] 11/72-1/74)

Skin Grafts, Crush Injury

Study ID (Location)	Study	Patient Characteristics	Treatment & Comparator	Nos	Outcome	Ref (Date)
1 (France)	Effect of HBOT in healing of soft tissue in crush injuries.	Patients with severe limb injury. Surgical management within 6 hours of injury. Exclusions: Pregnancy, contraindications, enrolment in other trial. Mean age: HBO 25.8 (16.1)Control 51.5 (20.9)Treatment 24 hrs after surgery.	HBO 2.5 atm abs, 90 minutes twice daily for six days. Placebo 1.1 atm abs	18 18	Wound healing, major surgery, time of healing, length of stay.	Bouchour et al [55] 1996
32 (UK)	Effect of HBOT on skin graft survival	Every patient presenting for split skin graft. Infants excluded. Time to treatment not defined.	HBO 2 atm abs 2 hours on evening of operation and twice daily for three days. Conventional treatment	24 24	Patches applied. % survival.	PerrinsDJD [54] 1967

11 References

1. Wilson, RC, Saunders, PJ, Meads, C, and Smith G. Carbon monoxide poisoning in the West Midlands Report of the Disease Surveillance Unit. 1997. Birmingham, University of Birmingham.

2. Wilson R, Saunders P. An epidemiological study of acute carbon monoxide poisoning in the West Midlands. *Occupational and Environmental Medicine* 1998;**55**:723-728.

3. Weaver, LK. Review of Hyperbaric Oxygen Therapy. 4-3-2000. Personal Communication

4. Leach R, Rees P, Wilmhurst P. Hyperbaric oxygen therapy. *British Medical Journal* 1998;**317**:1140-1143.

5. Grim P, Gottlieb L, Boddie A, Batson E. Hyperbaric Oxygen Therapy. *Journal of the American Medical Association* 1990;**263**:2216-2221.

6. Huston C. Carbon monoxide. *American Journal of Nursing* 1996;**96**:48

7. Tibbles P, Edelsberg J. Medical Progress: Hyperbaric-oxygen therapy. *New England Journal of Medicine* 1996;**334**:1642-1648.

8. Tibbles, PM. Hyperbaric Oxygen. 29-2-2000. Personal Communication

9. The British Hyperbaric Association. Register of Member Chambers. 1998. Great Yarmouth, The British Hyperbaric Association.

10. Gabb G, Robin E. Risk benefit analysis in chest medicine. *Chest* 1987;**92**:1074-1082.

11. Sheffield P, Desautels D. Hyperbaric and hypobaric chamber fires: a 73-year analysis. *Undersea & Hyperbaric Medicine* 1997;**24**:153-164.

12. Simini B. Fire fuels concern over hyperbaric oxygen facilities. *Lancet* 1997;**350**:1375

13. Trytko B, Bennet M. Complication rates are much lower than authors suggest. *British Medical Journal* 1999;**318**:1077

14. Mitton, C and Hailey, D. Hyperbaric oxygen treatment in Alberta. 1998. Alberta Heritage Foundation for Medical Research and the University of Calgary.

15. Balzan M, Agius G, Galea Debono A. Carbon monoxide poisoning: easy to treat but difficult to recognise. *Postgraduate Medical Journal* 1996;**72**:470-473.

16. Charlton J, Kelly S, Dunnell K, Evans B, Jenkins R, Wallis R. Trends in suicide deaths in England and Wales. *Population Trends* 1992;**69**:10-16.

17. Lewis R. Carbon monoxide. In: Lewis, ed. *Sax's Dangerous Properties of Chemicals*. New York: Van Nostand Reinhold, 1996;

18. Chance B, Erechinska M, Wagner M. Mitochondrial responses to carbon monoxide toxicity. *Annals of the New York Academy of Sciences* 1976;193-204.

19. Soden K, Marras G, Amsel J. Carboxyhemoglobin levels in methylene chloride exposed employees. *Journal of Occupational and Environmental Medicine* 1996;**38**:367-371.

20. Carbon monoxide poisoning. http://www.hse.gov.uk/gas/main/htm 1-1-2000.

21. Center for Disease Control. Unintentional carbon monoxide poisoning from indoor use of pressure washers-Iowa, January 1992-January 1993. *Journal of the American Medical Association* 2000;**270**:2034-2037.

22. Hampson N, Norkool D. Carbon monoxide poisoning in children riding in the back of pickup trucks. *Journal of the American Medical Association* 1992;**267**:538-540.

23. BBC Radio Five Live Magazine. 5-9-1996.

24. Ernst A, Zibrak J. Carbon monoxide poisoning. *Current Concepts* 1999;**339**:1603-1608.

25. Chale S. Carbon monoxide poisoning. In: Viccellio P, ed. *Handbook of Medical Toxicology 1st ed.* New York: Little, Brown and Company, 1993;639-647.

26. Winter P, Miller J. Carbon monoxide poisoning. *Journal of the American Medical Association* 1976;**236**:1502-1504.

27. Department of the Environment Expert Panel on Air Quality Standards. Carbon monoxide. 1994. London, HMSO.

28. Meredith T, Vale A. Carbon monoxide poisoning. *British Medical Journal* 1988;**296**:77-79.

29. Longo L. The biological effects of carbon monoxide on the pregnant woman, fetus and newborn infant. *American Journal of Obstetrics and Gynecology* 1977;**129**:69-103.

30. Koren G, Sharav T, Pastuszak A, et al. A multicentre, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. *Reproductive Toxicology* 1991;**5**:397-403.

31. Norman C, Halton D. Is carbon monoxide a workplace teratogen? A review and evaluation of the literature. *Annals of Occupational Hygiene* 1990;**34**:335-347.

32. Ilano A, Raffin T. Management of carbon monoxide poisoning. *Chest* 1990;**97**:165-169.

33. Weaver L. Carbon monoxide poisoning. *Critical Care Clinics* 1999;**15**:297-317.

34. Aitasalo K, Niinikoski J, Grenman R, Virolainen E. A modified protocol for early treatment of osteomyelitis and osteoradionecrosis of the mandible. *Head & Neck* 1998;**20**:411-417.

35. Brown D, Evans A, Sandor G. Hyperbaric oxygen therapy in the management of osteoradionecrosis of the mandible. *Advances in Oto-Rhino-Laryngology* 1998;**54**:14-32.

36. Wiseman D, Grossman A. Hyperbaric oxygen in the treatment of burns. *Critical Care Clinics* 1985; **1**:129-145.

37. Staley M, Richard R. Management of the acute burn wound: an overview. *Advances in Wound Care* 1997;**10**:39-44.

38. Compartment syndrome

http://www.orthopaedic.ed.ac.uk/compartment/tsld002.htm 31-1-2000.

39. Wessex Institute for Public Health Medicine. Hyperbaric Oxygen Therapy (for the management of gas gangrene, carbon monoxide poisoning, burns, soft tissue injury,and major wound healing). 1994. University of Southampton, Wessex Institute for Health Research and Development.

40. Tibbles P, Perrotta P. Treatment of carbon monoxide poisoning:a critical review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. *Annals of Emergency Medicine* 1994;**24**:269-276.

41. Sheps, SB. Hyperbaric oxygen for osteomyelitis and osteoradionecrosis. 92(3D). 1992. University of British Columbia, British Columbia Office of Health Technology Assessment.

42. Ducasse J, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? *Undersea and Hyperbaric Medicine* 1995;**22**:1-15.

43. Mathieu D, Wattel F, Mathieu-Nolf M, et al. Randomised prospective study comparing the effect of HBO versus 12 hours NBO in non comatose CO poisoned patients: Results of the interim analysis. *Undersea and Hyperbaric Medicine* 1996;**23**:7-8.

44. Raphael J, Elkharrat D, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *The Lancet* 1989;**2**:414-419.

45. Scheinkestel C, Bailey M, Myles P, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Medical Journal of Australia* 1999;**170**:203-210.

46. Thom S, Taber R, Mendiguren I, Clark J, Hardy K, Fisher A. Delayed neuropsychologic sequelae after carbon monoxide poisoning: Prevention by treatment with hyperbaric oxygen. *Annals of Emergency Medicine* 1995;**25**:474-479.

47. Weaver L, Hopkins R, Larson-Lohr V, Howe S, Haberstock D. Double blind, controlled, prospective randomised clinical trial in patients with acute carbon monoxide poisoning: outcome of patients treated with normobaric or hypobaric oxygen. An interim report. *Undersea & Hyperbaric Medicine* 1995;**22**:14

48. Weaver L. Randomised clinical trial In carbon monoxide poisoning needed. *American Journal of Emergency Medicine.* 1994;**12**:687-688.

49. Marx R, Johnson R, Kline S. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *Journal of the American Dental Association* 1985;**111**:49-54.

50. Tobey RE, Kelly JF. Osteoradionecrosis of the jaws. *Otolaryngologic Clinics of North America* 1979;**12**:183-186.

51. Brannen A, Still J, Haynes M, et al. A randomised prospective trial of hyperbaric oxygen in a referral burn centre population. *The American Surgeon* 1997;**63**:205-208.

52. Hart G, Broussard N, Goodman D, Yanda R. Treatment of burns with hyperbaric oxygen. *Surgery, Gynecology & Obstetrics* 1974;**139**:693-696.

53. Niezgoda J, Cianci P, Folden B, Ortega R, Slade J, Storrow A. The effect of hyperbaric oxygen therapy on a burn wound model in human volunteers. *Hyperbaric oxygen therapy for burns* 1989;**99**:1620-1625.

54. Perrins D. Influence of hyperbaric oxygen on the survival of split skin grafts. *The Lancet* 1967;868-871.

55. Bouachour G, Cronier P, Gouello J, Toulemonde J, Talha A, Alquier P. Hyperbaric oxygen therapy in the management of crush injuries: a randomised double-blind placebo-controlled clinical trial. *Journal of Trauma* 1996;**41**:333-339.

56. Cronier P, Bouachour G, Talha A, Gouello J, Toulemond J, Merienne. The effectiveness of hyperbaric oxygen in post-traumatic skin lesions. *Journal of Bone and Joint Surgery* 1997;**79-B**:56

57. Wilson, RC. Hospital beds. 20-10-1999. Personal Communication

58. Lowe-Ponsford F. Clinical aspects of carbon monoxide poisoning. *Adverse Drug reaction & acute poisoning* 1989;**8**:217-240.