Manchester Metropolitan University

Evidence for the use of Hyperbaric Oxygen Therapy (HBOT) A Review

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Introduction

The purpose of this review was to assess the evidence for the use of HBOT to treat soft tissue injuries, including DOMS, and closed fractures. It was a report commissioned by City Football Services to help understand whether using HBOT was safe, effective, what parameters are required and what conditions could be treated using HBOT.

HBOT Theory

Hyperbaric oxygen therapy (HBOT) is a process involving the use of a hyperbaric chamber to reach pressures greater than local atmospheric pressure to treat injury or disease (Sjoberg & Singer, 2013). The therapy is carried out using mono-place (single person) or multi-place (multiple person) chambers. Multi-place chambers are pressurised by air, and oxygen is delivered via a face-mask, endotracheal tubes or head hoods. Near 100% oxygen is used to pressurise smaller mono-place chambers and thus the patient directly breathes the ambient chamber oxygen.

The pressure of the surrounding medium, such as gas or liquid, coming into contact with the object is known as ambient pressure. This pressure is measured using the pascal (Pa). When using hyperbaric therapy ambient pressure is more commonly measured in atmospheres (ATA or ATM). Atmospheric pressure at sea level is 1 ATA; at 10m depth in sea water is 2 ATA; and at 20m depth is 3 ATA (Mills, 2012). According to the Undersea & Hyperbaric Medical Society (UHMS) in order to constitute HBOT, the person must inhale 100% oxygen with pressurisation at 1.4 ATA or higher (Hampson, 1999). The restorative effects of HBOT are the result of an elevation in dissolved oxygen in plasma and tissue oxygen delivery (Thom, 2011). Delivery of 100% oxygen over or equal to 60 minutes with a pressure at 1.4 atmospheric absolute (ATA) has previously been reported to be beneficial for the rate of recovery after injury (Thom, 1992).

Physiological and biochemical effects of HBOT

The efficacy of HBOT is established through the biochemical and physiological effects of hyperoxia. The effect of HBOT is based on the gas laws: Daltons, Boyle's and Henry's Law (Gill & Bell, 2004) Henry's law is the basis for elevated tissue oxygen tensions found with HBOT, stating that, "At a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid or tissue is directly proportional to the partial pressure of that gas in equilibrium with that liquid or tissue."

Oxygen is transported by blood chemically binding to haemoglobin and physically by dissolving in plasma. During normal respiration at atmospheric pressure the oxygen bound to haemoglobin has an oxygen saturation of 97-99%. The additional oxygen carried within the plasma as a result of Henry's law, further enhances the oxygenation of tissues. The arterial oxygen tension and tissue oxygen tension are 100 millimetre of mercury (mmHg) and 55 mmHg, respectively, with a plasma oxygen concentration of 3ml/l, when breathing normobaric air (normal barometric pressure equivalent to that at sea level). However, when at a hyperbaric level; e.g. 100% oxygen at 3 ATA, arterial oxygen tension and tissue oxygen tension are increased to approximately 2000 mmHg and 500mmHg, respectively, with a dissolved plasma oxygen concentration close to 60 ml/l (Leach et al, 1998). In conditions where haemoglobin oxygen carriage is obstructed, the oxygen carried within the plasma is able to pass.

Research into the physiological effects of hyperoxia has found that blood flow is suddenly reduced as a result of the sudden vasoconstriction of vessels. However, with increased oxygen plasma carriage through use of HBOT, blood flow to ischaemic tissue is enhanced. Increased levels of post-traumatic, tissue oedema found in compartment syndrome and crush injuries, can be significantly reduced with the assistance of vasoconstriction (Mortensen, 2008). Additional HBOT short term effects include an elevated leukocyte function and phagocytosis by improving the local microcirculation through the destruction of bacteria, all contributing to the anti-inflammatory effect. Late stage healing effects contribute to neovascularization (expansion of microvascular networks), through synthesis of growth factors and angiogenesis (local endothelial cells aid growth of new blood vessels) (Simsek et al, 2011). HBOT also stimulates synthesis of fibroblast collagen

production and osteogenesis (Hunt, 1990, Zamboni et al, 1993; Hopf & Rollins, 2007; Soneja et al, 2005; Bosco et al, 2009).

HBOT Mechanisms of Action:

- Reactive Vasoconstriction: Oedema is reduced whilst normal tissue oxygen is maintained through the contraction of small vessels that are constricted (Mortensen, 2008).
- Healing effect: improves and intensifies the growth of osteoclasts and osteoblasts, increases the synthesis of collagen and encourages angiogenesis in hypoxic tissues, thus increasing healing in chronic wounds osteradionecrosis and burns (Kang et al, 2004).
- Oxygen pressure increase: aids removal of toxic gases (carbon monoxide) because when high concentrations of oxygen are present in alveolar air carbon monoxide is displaced from haemoglobin faster than ambient air pressure (Weaver et al, 2002; Garrrabou et al, 2011).
- Antibacterial effect: - ensures oxygenation of antibacterial defences (Kendall et al, 2012).
- Action: Gas embolism and decompression sickness is treated by reducing the pressure volume of gas bubbles (Thom, 2008).

The incidence of sporting injuries has increased as a result of the increased intensity of elite and recreational competitive sport. These sporting injuries may include fractures to the bone, and /or muscle, ligament and tendon damage.

Reduced stability, significant gaps at the fracture site, infection, reduced vascularity all impede the fracture healing process. Treatment aims to improve the structural integrity of the fracture site. However, the management of fractures can be frequently impaired as a result of delayed or non-union, leading to a significant loss of function (Birnbaum, 2002).

A number of treatment approaches have been adopted to establish osteogenesis (bone generation), provide stability and reduce fracture gaps. Methods used include internal and external fixation, bone grafting electrical stimulation and extracorporeal shockwave therapy (Gallay & Mckee, 2000; Biedermann et al 2003; Karamitros et al, 2006). HBOT has been used in the past for treatment of bone fractures but the evidence support its positive effect remains anecdotal.

Injuries affecting the soft tissue are common and may include anything from minor bruising to serious damage to the ligament, tendon and muscles. The cause of such injuries may range from overuse and repetitive strain to traumatic injuries. In addition, and commonly as a result of unaccustomed exercise, is delayed onset of muscle soreness (DOMS) which may present as slight muscle soreness up to significant pain and swelling.

The potential of HBOT to accelerate the healing process through the reduction of inflammation and local tissue hypoxia has interested the sports medicine field. Despite no conclusive scientific evidence to support the use of HBOT for sports injuries, hyperbaric chambers have been purchased by a number of professional sport facilities. HBOT was seen as a treatment approach to accelerate the recovery process, enabling the athlete to return to competition / training.

What Is HBOT Used For?

Hyperbaric oxygen therapy is used in the treatment of a number of conditions; in some cases it may be used as the primary therapy intervention, whereas in others as an adjunct to pharmacology or surgery. Cochrane reviews have addressed the use of HBOT in a number diseases / conditions (Kranke et al, 2012; Eskes et al, 2013; Levett et al, 2015). However, in general, the quality and number of trials have been considered insufficient to draw definite conclusions (Sjoberg & Singer, 2013).

The US Food and Drug Administration (FDA) and UHMS has cleared 14 indications for the safe use of HBOT. Idiopathic sudden sensorineural hearing loss being the most recent addition having been approved on October 2011 by the UHMS. Oxygen has often been used, and its efficacy claimed, without the need to titrate the dose (Sjoberg & Singer, 2013).

Due to the limited evidence to support the use of HBOT for closed soft tissue injury, DOMS and fractures, they have not been cleared by the FDA and UHMS.

Air or Gas Embolism

Air or gas embolism occurs when air bubbles form in the circulation. A common cause is pulmonary barotrauma which can be seen on returning to the surface after breathing compressed gas at depth (in water), and also during mechanical ventilation (Murphy et al, 1985; Hampson 1999).

As stated in Boyle's law, the volume of gas is inversely proportional to pressure, the bubble volume is reduced with increased pressure (Benson et al, 2003). Case studies and UHMS suggests that there is 100% oxygen at 2.8 ATA. Repeating using these parameters for 5 to 10 treatments until no evidence of further improvement would offer the greatest benefit for the treatment of air or gas embolism, as recommended by the UHMS (Hampson, 1999 & Benson et al, 2003 Gesell, 2008).

Carbon Monoxide Poisoning

Carbon monoxide poisoning can cause many delayed neurological problems including chronic headaches, cognitive deficits and Parkinson's Disease (Thom et al, 1995, Weaver et al, 2002).

HBOT helps to separate carbon monoxide from haemoglobin and increases the oxygenation of tissues and helps decrease the incidence of delayed neuropsychological sequelae (Thom, 1995; Leach et al, 1998). Recommended parameters used during previous research and recommended by UHMS are 100% oxygen and between 2.4 ATA and 3.0 ATA. Number of session suggested - until symptoms resolved (Thom et al, 1995 & Hampson, 1999, Gesell 2008).

Clostridial Myositis and Myenonecrosis (Gas Gangrene)

Clostridial myositis and myenonecrosis is an acute rapid invasive infection of the muscles causing oedema, tissue destruction and toxemia (Stevens, 2000). The infection is caused by germinating clostridial spores within the tissue (Stevens, 2000). HBOT is used in addition to tissue debridement to help reduce bacteria and toxins. Treatment in the first 24hrs should include 3 x 90 minute treatments with 100% oxygen at 3 ATA. It is suggested that the initial treatments should be followed by twice-daily treatments for a further 4-5 days (Hampson, 1999; Gesell, 2008).

Crush Injury, Compartment Syndrome and other Acute Traumatic Ischaemias

Crush injuries can involve multiple tissue trauma including joints, bones, tendons, muscles and skin. Further complications following trauma may arise including: non-union of fractures, osteomyelitis, compartment syndrome and failed flaps (Wattel et al, 1998). HBOT is used to regain tissue oxygen tensions through the increase of plasma-based oxygenation, in addition to stimulating the synthesis of collagen and fibroblast facilitating angiogenesis (Zamboni et al, 1993, Strauss et al, 1983).

With the introduction of hyperoxia in conditions such as compartment syndrome the cycle of ischaemia and oedema is resolved without impairing the delivery of oxygen as a result of

vasoconstriction (Nylander et al, 1985). Treatment is carried out once per day for several days dependent on the level of injury and advised to take place within 4-6hrs post injury using 100% Oxygen at 2.0 - 2.5 ATA once per day (Hampson, 1999; Gesell, 2008).

Decompression Sickness

Decompression sickness occurs when, due to supersaturation, inert gas (commonly nitrogen) forms within the tissue and capillaries (Brubakk, 1999). Supersaturation and bubble formation occurs when the inert gas partial pressure of the tissues exceeds the ambient pressure (Carturan et al, 2002). Symptoms can include joint pains, neurological complaints, shock and death as a result of the occlusion of vessels and tissue disruption (Hagberg & Ornhagen, 2003).

Using HBOT to administer oxygen at greater ambient pressure is said to reduce the bubble volume (Zamboni, 1993). HBOT repeated up to 10 times of 100% oxygen at 2.8 ATA has been recommended (Hampson, 1999, Gesell, 2008).

Arterial insufficiencies - Enhancement of healing in selected problem wounds

HBOT is frequently used for the treatment of problem wounds including insufficiency ulcers and diabetic foot ulcers (Abidia et al, 2003).Healing is impaired by a reduction in bacterial killing, phagocytosis and lymphocytes (WBC) (Simsek et al, 2011).

HBOT at 100% oxygen and increased atmospheric pressure results in an increase plasma volume and therefore transportation of oxygen enhancing wound healing through increased oxygenation, fibroblast growth, collagen synthesis and neovascularisation (Baroni et al, 1987 & Hunt, 1990).

Significantly higher rates of wound healing were found using HBOT following a randomised controlled trial (RCT) including 100 patients with diabetic foot ulcers, that had failed to respond to

other treatments (Duzgun et al, 2008). These findings have been supported by further RCTs demonstrating wound healing and wound size reduction (Londahl et al, 2010 & Ma et al, 2013).

UHMS recommend 90-120mins, once a day, up to 30 treatments of 100% oxygen at 2.0-2.5 ATA (Hampson 1999; Gesell, 2008). These parameters were also used during RCTs (Abidia et al, 2003 & Ma et al, 2013)

Severe Anaemia

A major loss of red blood cells causing limited oxygen carriage as a result of haemolysis or haemorrhage results in tissue hypoxia leading to ischaemia (Leach et al, 1998). In these situations, and where transfusions are not possible, e.g. rare blood group or religious beliefs, HBOT may be used to increase levels of oxygen dissolved in plasma, compensating for reduced haemoglobin levels.

Treatment periods of 2 - 4 hours, three to four times per day of 100% oxygen up to 3 ATA have been recommended by the UHMS (Hampson, 1999, Gesell, 2008)

Intercranial Abscess

Improved diagnosis and therapy in conditions including subdural empyema, cerebral abscess have decreased the mortality rate related to them. HBOT may be used in circumstances where patients have failed to respond to standard care. HBOT can modify the immune response and reduce cerebral oedema.

Despite limited clinical evidence UHMS recommend treatment sessions between 60-90 minutes of 100% oxygen at 2.0-2.5 ATA and up to 20 sessions (Hampson, 1999; Gesell, 2008).

Necrotising Soft Tissue Infections

Necrotising soft tissue infections are infections of the deep fascia in addition to involvement of subcutaneous and cutaneous layers. Tissues become hypoxic, hypo-cellular and hypo-vascular. A Cochrane review on adjunctive hyperbaric oxygen for necrotising fasciitis (Levett et al., 2015) screened 673 records and found no studies eligible for assessment. A retrospective cohort study found limb salvage and improved survival from necrotising soft tissue infection using HBOT (Wilkinson & Doolette, 2004).

UHMS recommends 100% oxygen at 2.0-2.5 ATA twice a day, with a reduction to one per day when symptoms are reduced. The recommendation is to treat until symptoms are resolved with a review at 30 sessions (Hampson, 1999, Gesell, 2008).

Osteomyelitis (Refractory)

Osteomyelitis is a bacterial infection of the bone. HBOT has been recommended in cases of osteomyelitis, in addition to debridement and antibiotics (Hampson, 1999, Gesell, 2008). Standard treatment for Osteomyelitis is antibiotic prophylaxis and surgical debridement (Gill & Bell, 2004; Eckardt et al, 1994).

Oxygen tension in normal bone under ambient conditions is approximately 45mmHg. In bone with chronic osteomyelitis a 50% reduction in oxygen tension has been reported (Galhoun et al, 1991). In order to maintain neovascularisation oxygen tensions of 30 to 40 mmHg are required (Hohn et al, 1976).

HBOT increases tissue oxygen tension increasing the synthesis of collagen and angiogenesis (Knighton et al, 1981). It has been reported that as a result of hypoxia and associated alterations in

oxygen tensions, osteoclast (re-absorbs bone) formation is increased and osteoblast (forms bone) activity is suppressed. HBOT is said to restore the elevated oxygen tension in infected bone and in hypoxic tissue anaerobic organism growth is inhibited (Davies et al, 1986).

HBOT, wound debridement and antibiotics proved successful in freeing 34 out 38 patients from osteomyelitis for a period of 34 months (Davis, et al, 1986). In a retrospective study by Chen et al (2003) 11 out of 14 patients with tibial osteomyelitis were treated successfully and safely with HBOT.

The number of sessions is usually defendant on the osteomyelitis severity. In conjunction with antibiotics, debridement the UHMS recommends daily treatments from 90-120mins of 100% oxygen at 2.0-2.5 ATA and up to 40 treatments (Hampson, 1999; Gesell, 2008).

Delayed Radiation Injury (soft tissue and bone necrosis)

Radiotherapy is used in high doses to eliminate tumours often causing a degree of cellular impairment, leading to tissue hypoxia. Osteoradionecrosis (ORN) is consistent with head and neck cancer patients receiving high doses of radiation. HBOT may be used to treat and halt the progression of ORN, increasing tissue oxygen tensions to sufficient levels to enable angiogenesis and improved leukocyte function (Hunt, 1990).

The evidence for the use of HBOT for delayed radiation injury is extensive albeit limited to lower levels of evidence. In a study comparing penicillin to HBOT Marx et al, (1985) found HBOT to be more effective in the prevention of osteonecrosis before tooth extraction. A review by Lubek et al, (2013) on the value of HBOT in treating ORN suggested that guidelines for the effective use of HBOT have yet to be established.

Evidence remains limited and there is only one prospective, double blinded, randomised, controlled trial comparing HBOT with placebo for mandibular ORN. As there was no evidence to support the

effectiveness of HBOT the trial was discontinued (Annane et al, 2004). 56% of patients with exposed bone were included in the study, a small sample size and HBOT not being standardised in the experimental group led to criticism of the study (Lubek et al, 2013).

Despite the existence of no clear evidence to support the use of HBOT in the treatment of delayed radiation therapy it has been recommended by UHMS that 100% oxygen at 2.0-2.5 ATA with sessions lasting 90-120 minutes for up to 40 days be administered (Hampson, 1990; Gesell, 2008).

Compromised Grafts and Flaps

HBOT has been established as a proven means of skin flap and graft survival in a number of animal studies (Baynosa & Zamboni, 2012). In tissues compromised by decreased perfusion or hypoxia, HBOT can be useful in flap / graft salvage.

A number of clinical studies have denigrated the effective use of HBOT when managing compromised skin flaps and grafts (Perrins, 1967; Gonnering et al, 1986; Waterhouse et al, 1993).

It is recommended that HBOT of 100% oxygen for 90 - 120 minutes at 2.0 - 2.5 ATA be used for compromised skin flaps and grafts with 2 treatments per day, before reducing to 1 per day on stabilisation of graft and treatment review after 20 treatments (Hampson, 1990; Gesell, 2008; Baynosa & Zamboni, 2012).

Acute Thermal Burn Injury

Insufficient oxygen and nutrient supply leads to a rapid deterioration to a central area of coagulation found with severe burns (Bhutani & Vishwanath, 2012). Initial therapy aims to preserve borderline tissue, reduce oedema, improve local host defences and promote wound closure. Usual care includes antibiotics, debridement and respiratory care.

As mentioned, hyper-oxygenation increases vasoconstriction of vessels and therefore decreases oedema enhances the formation of collagen and angiogenesis (Zamboni et al, 1993). Despite a number of studies that support the use of HBOT in thermal burns, recent reviews report insufficient level of evidence to provide clear practice guidelines (Villanueva et al, 2009; Cianci et al, 2013).

It has been suggested that HBOT is commenced as soon as possible following injury and with three sessions within 24hrs. Treatment has been recommended twice daily with 90 minutes per treatment at 2.0 - 2.4 ATA (Hampson, 1990; Gesell, 2008; Cianci et al, 2013).

Idiopathic Sudden Sensorineural Hearing Loss

Idiopathic sudden sensorineural hearing loss (ISSHL) is an hearing impairment with sensorineural hearing loss greater than 30 dB in three sequential frequencies occurring over three days (Hughes, 1996). The exact cause of ISSHL is unknown and it has been suggested that a number of pathogens maybe involved including, viral infections, inner ear membrane rupture, trauma, toxins, autoimmune disease and vascular occlusion (Thurmond & Amedee, 1998).

A number of different treatments have been proposed, without large randomised controls to support their use. Administration of steroids has been one of the most frequently utilised treatment approaches, although studies to support its use are poor (Labus et al, 2010). ISSHL was added to the UHMS list of indications for HBOT therapy, approved by the UHMS Board of Directors on October 8th 2011 (Nikitopoulou & Papalimperi, 2015).

The use of HBOT has been proposed because it has been suggested that hearing loss may be the result of hypoxia or other inflammatory processes leading to ischeamic changes effecting the cochlea apparatus function (Mazurek et al, 2006). In the event of reduced oxygenation to structures within the cochlea, the oxygen concentration would be restored using HBOT (Pezzoli et al, 2015).

Recommended treatment parameters for the use of HBOT for ISSHL are 100% oxygen at 2.0 - 2.5 ATA for 90 mins per day for up to 10 - 20 sessions dependent on the duration of symptoms and the severity (Hampson, 1999; Gesell, 2008)

Summary of the uses of HBOT

The use of HBOT to treat a number of medical has been recommended despite the varied evidence base. Of the 14 conditions accepted by FDA and the UHMS the evidence for air embolism and decompression is well established and stronger than the other 12 conditions. Despite a number of other suggested indications for HBOT, including sports injuries, fracture healing and bone grafting, head injuries, spinal cord injuries, the evidence remains, albeit extensive, weak, lacking in randomised controlled trails and largely anecdotal. In order to establish the efficacy in other conditions further research is required.

The Safety of HBOT

Although considered a relatively safe treatment, with rare complications, due to the hyperoxic effect and increased pressure involved, HBOT does bring some risks (Leach, 1998). Although severe side effects and life threatening cases are rare, HBOT cannot be considered an entirely safe clinical intervention (Bennett at al, 2012).

One of the most common side effects lasting anywhere from weeks up to months following HBOT is reversible myopia, which occurs as a result of the toxic oxygen on the lens of the eye, (Leach et al, 1998). Other reported general features include claustrophobia, fatigue, vomiting and headache. Claustrophobia is more commonly seen in mono-place (single person) chambers. Mono-place chambers also carry an increased fire risk, which is the most common fatal complication, as the whole chamber contains hyperbaric oxygen, which is not flammable or explosive but it would support combustion (Leach, 1998; Orsted & Poulson, 2012).

Other common and less severe problems include patient difficulty with pressure equalisation within the middle ear and sinus barotrauma (injury caused by a change in air pressure affecting typically the ear). To minimise barotrauma a reduced rate of compression / decompression is recommended. To further reduce the risk of barotrauma and the discomfort associated with it, an explanation on effective ear clearance should be provided (Fitzpatrick et al, 1999).

The increase in oxygen partial pressure may affect the glucose levels of diabetic patients.

A more serious complaint is pulmonary oxygen toxicity, which may result after continuously breathing 100% oxygen at sea level (1 ATA) over approximately 36 hours. Whereas when the pressure is increased to 2 ATA oxygen toxicity ensues after 6 hours (Kindwall, 2002).

With time periods reaching 3 hours and with pressures up to 3 ATA, oxygen toxicity no longer becomes the main problem as periods of time spent at these parameters is likely to result in seizure (Kindwall, 2002).

Repeated HBOT treatments may result in drop in pulmonary function (Leach et al, 1998). However, it has been confirmed that oxygen tissue toxicity may be prevented by introducing air breaks approximately every 30 minutes to prevent the formation of free oxygen radicals (Leach et al, 1998; Kindwall, 2002). However, if the length of treatment is no longer than 120 minutes and pressure

does not exceed of 3 ATA and with the number of individual sessions no greater than 30 treatment is considered absolutely safe (Leach et al, 1998).

A number of studies have demonstrated that HBOT does not increase the reoccurrence nor does it promote the growth of tumours (Moen & Stuhr, 2012). A recent Cochrane review carried out to assess the benefits and harms of radiotherapy while breathing HBO found evidence that the control of tumours is improved (Bennett et al, 2012).

Contraindications for HBOT

Absolute Contraindications (Sharkey, 2000)

- **Untreated tension pneumothorax** - developing tension pneumothorax is highly probable with compression and decompression during HBOT (Bhutani & Vishwanath, 2012).
- **Certain Medications** - Some medications have been observed to become toxic during HBOT:
- Chemotherapeutic drugs
- Doxorubicin and Cisplatin
- Bacterial infection drugs;
- Mafenide acetate
- Treatment of alcoholism, Disulfiram (Smith, 2011)

Relative Contraindications:

- Upper respiratory tract infections
- Emphysema with carbon dioxide retentions
- Asymptomatic pulmonary lesions which are seen on X-ray
- History of thoracic or ear surgery
- Uncontrolled Hypothermia
- Pregnancy
- Claustrophobia
- Seizure disorder
- Presence of a cardiac pacemaker

Side Effects:

- Middle ear/pulmonary barotrauma
- Vomiting
- Cataract
- Fatigue
- Claustrophobia (Considered a contraindication but on occasions can occur during treatment and so can be regarded as a side effect)
- Oxygen toxicity:
    - Pulmonary
    - Central Nervous system – rare occurrence of seizures
- Hypoglycaemia
- Thrombocytopenia
- Respiratory failure
- Fire hazard
- Headache
- Disease as a result of rapid decompression
- Diabetes – sugar levels /cardiac history - attention given due to the vasoconstrictive effect of HBOT

Although the risk is minimal and usually reversible when using HBOT, the complications or contraindications have not been identified when used in clinical trials. A Cochrane review (Kranke et al., 2015) to assess the benefits and harms of adjunctive HBOT for treating chronic ulcers of the lower limb reported that of the five studies reviewed, three failed to report on the potential hazards or detrimental outcomes and two studies clearly stated that hyperbaric oxygen therapy carried no risks or complications.

In order to prevent harmful incidences associated with HBOT it is advised that patients with known complications should be identified to allow for the rate of compression and decompression to be altered accordingly.

A summary of the Safety of HBOT

The use of HBOT can be determined as safe, however, fire is always a possible hazard, but so long as extensive precautions are made, prevention is ensured. When procedures and protocols are strictly adhered to by the participants involved, potential risks are likely to be avoided.

Soft Tissue Healing and HBOT

Method:

Electronic searches of the following databases were undertaken:

- The Cochrane, Joint and Muscle Trauma Group Specialised Register (to September 2015)
- AMED (Allied & Complimentary Medicine. 1985 to September 2010),
- OVID MEDLINE (1946 to September Week 4),
- SPORTDiscus (1980 - present)
- Searched Reference lists of articles.

Key words used:

Soft tissue injuries, Humans, Sports injuries, athletic injuries, arm, leg, ligament, tendon, muscle, Hyperbaric oxygenation, oxygen, hyperbaric, chamber, monoplace, multiplace, randomised controlled trial, controlled clinical trial, controlled study, prospective study double blinded, single blinded.

All randomised and quasi-randomised controlled trials that compared HBOT with no HBOT (sham or no treatment) were included.

Patients with closed injuries to ligament, tendon or muscle tissue with the inclusion of DOMS.

No restrictions on gender or age were made.

Any standard HBOT treatment regimen using pressures 1.5 ATA - 3 ATA for 30 minutes to 60 minute individual treatment periods for promoting soft tissue or bone injury was accepted.

The search revealed 9 small trials, identified in the tables below. Of the nine trials, 7 examined the effect of HBOT on DOMS. Two of the trials, Staples 1999a and Staples 1999b, represent the first and second phase of the same study. The remaining 2 trials compared HBOT versus sham therapy on closed soft tissue injuries that included medial collateral knee ligament and ankle sprain.

A Cochrane systematic review was identified in the search. This study was initially conducted in 2005, with a new search for studies and content updated in 2010, although no changes to conclusions were made (Bennett et al, 2010).

The review describes the use and parameters of HBOT. The safety of HBOT will also be reviewed with particular focus on known side effects, contraindications to its use and the precautions required to ensure the safe use of HBOT. A review of HBOT for soft tissue injures, including DOMS, and fracture healing will be included. The article will concluded with recommendations for the use of HBOT and the implications for practice and future research.

FIGURE 1 SAFETY CONSIDERATIONS IN HBOT STUDIES FOR SOFT TISSUE INJURY

Author date / Methods	Pathology	Side effects Experienced	Precautions [Who should not have HBOT]	Recommendations [When not to use it]
Babul, 2003 Randomised. patient and assessor blind	Acute soft tissue injury - provocative exercise of non-dominant quadriceps muscle	Non reported	Individuals who had experienced quadriceps DOMS in 3 months prior to study or who had a past history of severe joint injury, arthritis or other chronic illness were excluded. Subjects taking analgesics or prescription drugs were also excluded	Not indicated
Borromeo, 1997 Randomised, patient and assessor blind. intention to treat analysis	Lateral ankle sprain within 72 hours	Increased pressure exposure or hyperbaric oxygen caused no adverse effects.	Contra-indications to HBOT	Subjects were excluded with severe asthma, active allergies, pulmonary disease, epilepsy, upper respiratory infections and pregnant.
Germain, 2003 Randomised, not blinded	Deliberately provocative exercise of the quadriceps muscle			
Harrison, 2001 Randomised, patient partial blinding	Deliberately provocative exercise of elbow flexors	Non reported	Health issues such as heart disease, diabetes and smoking that would exclude subjects from the study were evaluated using a physical health questionnaire	Health issues such as heart disease, diabetes and smoking that would exclude subjects from the study were evaluated using a physical health questionnaire
Mekjavic, 2000 Randomised, patient and statistician blind	Deliberately provocative exercise of elbow flexors	Non reported	Non reported	Non reported
Soolsma, 1996 Randomised, method not specified. Participant and assessor blind.	Grade II injury to the medial collateral ligament of the knee - presenting to an orthopaedic surgeon within 72 hours of injury	Non reported	Non reported	Non reported
Staples 1999a Randomised, participant blind and probably assessor blind	Deliberately provocative exercise of the non-dominant quadriceps muscle	Non reported	Recent respiratory tract infection / confinement anxiety	A physician assessed and excluded subjects considered incompatible to HBOT including: idiopathic lung cyst, pneumothorax, hyperinflation, any other lung problem, unresolved upper respiratory tract infection and if suffering a fever at the time of HBOT exposure.

Staples 1999b Randomised, participant and probably assessor blind	Deliberately provocative exercise of the non-dominant quadriceps muscle	Non reported		A physician assessed and excluded subjects considered incompatible to HBOT including: idiopathic lung cyst, pneumothorax, hyperinflation, any other lung problem, unresolved upper respiratory tract infection and if suffering a fever at the time of HBOT exposure.
Webster, 2002 Randomised, patients and assessor blind	Deliberately provocative exercise of the gastrocnemius muscle	Non reported	Inspection of subject eardrums for pathology took place before and after each hyperbaric treatment.	A physician examined the subjects to rule out any contraindications to hyperbaric therapy.

FIGURE 2 PICO TABLE FOR SOFT TISSUE STUDIES

Author date	N=	Population	Intervention	comparator	Outcomes	Results
Webster, 2002	12	healthy young male volunteers	100% oxygen at 2.5 ATA for 60 minutes at 3, 24, and 48 hours post injury	Sham HBOT at 1.3 ATA on air on the same schedule	PAIN SCORE Descriptor differential scale expressed as percentage changes compared to maximal pain. (data not used due to difficulties in interpretation STRENGTH change from baseline as maximal eccentric torque expressed as a percentage SWELLING percent change in cross-sectional area of medial gastrocnemius	The study found some evidence of a faster recovery of isometric torque and the reduction of pain and unpleasantness from days 2 to 5 post muscle damage using HBOT.
Germain, 2003	16	16 Healthy volunteers (10 females)	95% oxygen at 2.5 ATA for 100 minutes at 1 and 6 hours post injury, then 1 treatment the next day and 2 treatments on the next day separated by 6 hours.	nil specific therapy	PAIN SCORE: visual analogue scale (0-10) STRENGTH change from baseline - maximum eccentric torque in Nm SWELLING tape measurement	The two groups showed no significant differences.
Babul, 2003	16	healthy female volunteers	HBOT 100% oxygen at 2.0 ATA for 60 minutes at 4, 24, 48 and 72 post-injury	CONTROL Sham HBOT at 1.2 ATA on air on the same schedule	PAIN SCORE: visual analogue scale (0-10) STRENGTH change from baseline - maximum eccentric torque in Nm SWELLING tape measurement	Administration of HBOT after eccentric exercise demonstrated no effect on the elevation of the various signs and symptoms associated with muscle injury or DOMS. Variables investigated demonstrated no statistical significance

Mekjavic, 2000	24	healthy male volunteers	HBOT standard exercise protocol followed by 7 sessions in 100% oxygen for 60 minutes daily at 2.5 ATA	CONTROL standard exercise protocol followed by 10 sessions in a sham hyperbaric treatment (2.5 ATA, 8% oxygen for 60 minutes) once daily	PAIN SCORE visual analogue scale (0-10) STRENGTH Change from baseline as maximal isometric strength in kilopascals before and for 10 days following exercise. measured by blinded researcher SWELLING arm circumference (cm)	HBOT is not considered effective as a treatment for DOMS
Soolsma, 1996	19	19 participants (5 females)	HBOT within 96 hours of injury - at 2.0 ATA on 100% oxygen for 60 minutes, 10 sessions over 2 weeks Regular icing, stretching and strengthening exercise rehabilitation program	Sham HBOT exposure to 1.2 ATA breathing air on the same schedule Regular icing, stretching and strengthening exercise rehabilitation program	SUBJECTIVE RECOVERY INDEX questionnaire PAIN SCORE visual analogue scale (0-10) RANGE OF MOTION ONE-LEGGED HOP TEST SWELLING measured with tape and volume by blinded researcher from MRI FIGURE OF EIGHT PERFORMANCE TEST time taken to complete a standard course - measured by blinded researcher	Patients treated with HBOT displayed a more rapid decrease in oedema volume, less muscle wasting, greater improvements in maximum flexion and greater range of movement. However, numbers allocated to each arm of this study were not reported
Staples 1999a	49	healthy male volunteers	HBOT (2 groups) 100% oxygen at 2.0 ATA for 1 hour at 0, 24, and 48 hours after exercise, followed by 2 sham treatments at 72 and 96 hours Sham at 0 and 24 hours, followed by HBOT at 48, 72 and 96 hours	CONTROL (2 groups) No specific intervention Sham HBOT by exposure to 1.2 ATA breathing air at 0, 24, 48, 72 and 96 hours for one hour on each occasion	PAIN SCORE Visual analogue: (0-10) STRENGTH change from baseline as maximal eccentric torque measured in Nm	No changes in pain were reported. Following the treatment it was suggested that HBOT may aid recovery from DOMS following eccentric quads exercise. A significant eccentric torque recovery was noticed in phase 1 and the 5 day treatment also showed a significant difference in phase 2.

Harrison, 2001	21	Healthy male volunteers	HBOT (2 Groups) Immediate HBOT: 100% 02 at 2.5 ATA for 100 mins. Treatments immediately post-injury and 24, 48, 72 and 96 hours. Delayed HBOT. Immediate sham (on air at minimal pressure) then the same schedule as above.	No specific therapy	PAIN SCORE verbally anchored 10 point scale STRENGTH change from baseline as maximum strength measured in kilograms SWELLING cross-sectional area estimated from MRI in mm2	The lack of significant differences suggest HBOT was not effective in treatment of exercise induced muscle injury
Staples, 1999b	30	Healthy male volunteers	HBOT (2 groups) 100% oxygen at 2.0 ATA for 1 hour at 0, 24, 48 hours after exercise, followed by two sham treatments at 72 and 96 hours. Same HBOT on five occasions at 0, 24, 48, 72 and 96 hours	CONTROL Sham HBOT by exposure to 1.2 ATA breathing air at 0, 24, 48, 72, and 96 hours	PAIN SCORE Visual analogue (0-10) STRENGTH change from baseline as maximal eccentric torque measured in Nm	No changes in pain were reported. Following the treatment it was suggested that HBOT may aid recovery from DOMS following eccentric quads exercise. A significant eccentric torque recovery was noticed in phase 1 and the 5 day treatment also showed a significant difference in phase 2.
Borromeo, 1997	32	32 adults (11 females)	HBOT at 2.0 ATA on 100% oxygen for 90 minutes. Posterior splint, crutches, NSAID, AROM exercise, ankle stirrup	Sham HBOT exposure to 1.1 ATA breathing air for 90 minutes	HEALED TO FINAL FOLLOW UP TIME TO NO FURTHER SYMPTOMS FUNCTIONAL SCORE PAIN SCORE: VAS (0-10) SWELLING: water displacement volumeter	No significant differences in oedema, pain, passive/active ROM or recovery time were found. However, an improvement in joint function was demonstrated in the HBOT group (95% CI 0.15 - 2.65; p=0.03).

FIGURE 3 USES / PARAMETERS FOR HBOT IN CLOSED SOFT TISSUE

Author / date	Pathology	%O2	Atmospheres Absolute	Duration	N of sessions
Babul, 2003	Provocative of non-dominant quadriceps muscle	100%	2.0 ATA	60 minutes	4 sessions 4, 24, 48 and 72 hours post injury
Borromeo, 1997	Lateral ankle sprain within 72 hours	100%	2.0 ATA	90 minutes	3 sessions over 7 days
Germain, 2003	Deliberately provocative exercise of the quadriceps muscle	95%	2.5 ATA	100 minutes	5 sessions at 1 and 6 hours post injury, then 1 treatment the next day and 2 treatments on the next day separated by 6 hours
Harrison, 2001	Deliberately provocative exercise of elbow flexors	100%	2.5 ATA	100 minutes	5 sessions post injury and 24, 48, 72 and 96 hours
Mekjavic, 2000	Deliberately provocative exercise of elbow flexors	100%	2.5 ATA	60 minutes	7 daily sessions
Soolsma, 1996	Grade II injury to the medial collateral ligament of the knee - presenting to an orthopaedic surgeon within 72 hours of injury	100%	2.0 ATA	60 minutes	10 sessions over 2 weeks
Staples 1999a	Deliberately provocative exercise of the non-dominant quadriceps muscle	100%	2.0 ATA	60 minutes	3 sessions at 0, 24 and 48 hours
Staples 1999b	Deliberately provocative exercise of the non-dominant quadriceps muscle	100%	2.0 ATA	60 minutes	2 groups at 0, 24, 48hours after exercise, followed by two sham treatments at 72 and 96 hours 0, 24, 48, 72, and 96 hours
Webster, 2002	Underwent deliberately provocative exercise of the gastrocnemius muscle	100%	2.5 ATA	60 minutes	3 sessions 3, 24 and 48 hours post injury

A Review of the Use of HBOT for Soft Tissue Repair

Borromeo et al., (1997)

A randomised, double-blinded study was carried out by Borromeo et al, (1997), to determine the effects of HBOT in the rehabilitation process following ankle sprains. The study observed a total of 32 patients allocated between HBOT, receiving 100% oxygen at 2 ATA for 90 mins for the first session and 60mins for the further two sessions. The placebo group received ambient air at 1.1 ATA for the same time periods and number of sessions. Both groups received three sessions over 7 days and the same standardised treatment. No significant differences in oedema, pain, passive/active ROM or recovery time were found. However, an improvement in joint function was demonstrated in the HBOT group (95% CI 0.15 - 2.65; p=0.03). No explanation of the randomisation procedure was carried out which may question the bias of the study. No patients were lost to follow up. From initial injury there was a reported 34 hour delay before the patient received treatment which may have influenced the potential influence of HBOT in this study. No complications were reported in this study.

Soolsma et al, (1996)

Soolsma et al, (1996), examined the use of HBOT to determine whether it will influence the rate of recovery from a grade II medial collateral ligament injury of the knee. They carried out a double blinded study with 19 patients, presenting within 72 hours of injury, of whom 14 finished the clinical assessment. The MRI investigation was completed by only 9 patients. The number of patients allocated to each group was not reported. The HBOT group received 100% oxygen at 2 ATA for 1 hour and the control group received room air at 1.2 ATA for 1 hour both treatments over 10 days. Patients treated with HBOT displayed a more rapid decrease in oedema volume, less muscle wasting, greater improvements in maximum flexion and greater

range of movement. However, numbers allocated to each arm of this study were not reported. No explanation of randomisation procedure was given.

Staples et al, (1999a) and Staples et al, (1999b) reported in same study: phase 1 and phase 2

Using a randomised, controlled, double-blind, prospective study of 66 untrained men, Staples et al, (1999), aimed to determine whether recovery from DOMS was enhanced using intermittent exposures of HBOT. Following exercise to produce muscle soreness the subjects were randomised to one of four groups; control, HBOT, delayed HBOT and sham, over a period of 5 days for the first phase. In the second phase there were three groups consisting of 5 days of treatment, 3 days of treatment and sham treatment. The HBOT group received 100% oxygen at 2 ATA for 1 hour and the sham received 21% oxygen at 1.2 ATA for 1 hour. No changes in pain were reported. Following the treatment it was suggested that HBOT may aid recovery from DOMS following eccentric quads exercise. A significant eccentric torque recovery was noticed in phase 1 and the 5 day treatment also showed a significant difference in phase 2. The study reported subject randomisation but failed to offer an explanation of the procedure used. The protocol for this study was complex and the design wasn't fully clear; 4 subjects were rejected after they displayed an increase in strength after the exercise protocol, 13 subjects were not reported on and the study was not completed by 9 subjects.

Mekjavic et al, (2000)

In this study of 24 healthy males with induced DOMS, the participants were randomised to the HBOT group or the placebo group. No difference in muscle strength recovery or pain was reported after HBOT. The parameters used were 100% oxygen at 2.5 ATA for the HBOT group and 8% oxygen at 2.5 ATA, both lasting for 1 hour for a period of 7 days. There were no reports of participants lost to follow up or disruption of the protocol. As with a number of other studies this one failed to identify procedure of subject randomisation.

Harrison et al, (2001)

The effect of HBOT after inducing DOMS in 21 healthy males was studied comparing 3 groups; immediate HBOT, delayed HBOT and control. The HBOT groups received 100% oxygen at 2.5 ATA for 100mins, consisting of 3x30min in addition to two 5 min periods of 21.93% oxygen. Treatment for the immediate HBOT and control started at 2hrs, delayed group was given sham until HBOT commenced at 24hrs and they all received treatment daily for 4 days. The control group did not receive any specific treatment. The randomisation procedure was not identified.

Webster et al, (2002)

This study looked at the use of HBOT as a treatment following exercise induced muscle damage. The study involved concentric and eccentric exercise of the gastrocnemius in 12 healthy male volunteers. The HBOT group received 100% oxygen at 2.5 ATA and the sham group received atmospheric air at 1.3 ATA. Both groups received 3 sessions of 60 minutes at 2-4 hours at 24 hours and at 48 hours. The study found some evidence of a faster recovery of isometric torque and the reduction of pain and unpleasantness from days 2 to 5 post muscle damage using HBOT. Despite no losses to follow up the study sample was small.

Babul et al, 2003

Babul et al. (2003), conducted a small randomised, double blind study which included 16 female participants with the aim to determine whether HBOT aided the rate of recovery from exercise induced injury in the quadriceps muscle. The HBOT group received 100% oxygen at 2.0 ATA and the sham received 21% oxygen at 1.2 ATA, both for 60 minutes. Each received treatment at 4, 24, 48, 72 hours post injury. Reported data only included differences between HBOT and control instead of outcomes in each group.

Due to lack of data this study was not included in the Bennett et al, (2010) meta-analysis.

Germain et al, (2003)

This study randomly assigned 16 subjects (10 female and 6 male) into two un-blinded groups. The study aimed to determine whether HBOT accelerated the recovery of exercise induced muscle injury. The HBOT group received 95% oxygen at 2.5 ATA for 100 minutes for a total of five sessions and the control didn't receive any treatment. The two groups showed no significant differences. This again was a small sample from which one of the sample was lost to follow up and was not reported on.

Due to lack of data this study was not included in the Bennett et al, (2010) meta-analysis.

A summary of the Use of HBOT for Soft Tissue Repair

Of the studies identified in the search, five (Webster et al, 2002; Soolsma et al, 1996; Staples et al 1999a and 1999b; Borromeo et al, 1997) identified a potential benefit using HBOT. The remaining four studies suggested no significant differences (Germain et al, 2003; Babul et al, 2003; Mekjavic et al, 2000; Harrison et al, 2001).

Four studies suggested that HBOT may hinder DOMS recovery (Staples 1999a and 1999b; Mekjavic et al, 2000; Harrison et al, 2001). However, the identified studies were generally of poor methodological quality, with 2 studies failing to provide the number of each group. The majority of studies suggested randomisation but did not identify the procedure used, two studies (Babul et al, 2003; Germain, 2003) provided very limited data and one study had a number of aspects that remained unclear (Soolsma et al, 1996).

The lack of available randomised controlled trials on application of HBOT for the treatment of delayed onset muscle soreness and closed soft tissue injury make it difficult to evaluate its efficacy. In addition to this the studies often fail to include relevant control groups which may help to determine whether the effect is due to solely an increase in pressure or to a combination of pressure and the presence of oxygen. Optimum pressure, frequency and

duration of treatments should be considered in future trials. In order to determine the effectiveness of HBOT further RCTs with larger samples are required.

Critical appraisal of Bennett et al, (2010), Hyperbaric oxygen therapy for delayed onset of muscle soreness and closed soft tissue injury: A Cochrane Review

The Bennett et al, (2010), systematic review included nine trials on HBOT for delayed onset muscle soreness and closed soft tissue injury. We used the Critical Appraisal Skills Programme (CASP) checklist to appraise this review to enable the appraisers to make sound judgements on its trustworthiness and relevance. The CASP checklist is used to appraise the research evidence in practice, aid personal and professional decision making, and to help develop policy and guidelines. The methodological quality of the review was evaluated to identify signs of bias to help determine the validity of the review. In particular aim to identify an unbiased inclusion / exclusion criteria, whether the search for studies was detailed, exhaustive and multifaceted. Whether the studies included were of high methodological quality and reproducible. In understanding the quality of the review, the conclusions can be considered to be trustworthy.

CASP Checklist

1. **Did the review address a clearly focused question?**

Yes.

The objective was to assess the benefits and harms of HBOT for treating soft tissue injury, including delayed onset of muscle soreness (DOMS).

The objective of the study was clearly stated, in aiming to assess the evidence for the use of HBOT to treat soft tissue injuries including DOMS. With the main aim to determine whether HBOT safely improves and speeds up functional outcome after injury.

2. Did the authors look for the right papers?

Yes.

The authors used / considered any randomised or quasi-randomised clinical trials that compared HBOT with no HBOT.

The authors restricted the review to acute closed injuries involving muscle, ligament and tendon, and where the mechanism is unaccustomed use, trauma from a direct blow, strain or overuse injury.

Trials comparing HBOT with no treatment or sham alone and using alternative therapies as the comparator were considered.

Population included patients with DOMS following exercise or patients with closed injury to ligament, tendon or muscle.

3. Do you think all the important, relevant studies were included?

Yes.

The authors searched:

- The Cochrane bone, joint and muscle trauma group specialised register (to Feb 2010), the Cochrane Central Register of Controlled Trials, MEDLINE (1950 to February 2010), EMBASE (1980 to 2010 week 07), CINAHL (1982 to October 2008).
- An additional database that had been developed in the authors hyperbaric facility and reference lists of articles.

In addition, the authors also hand searched relevant journals and textbooks and made contact with researchers in the field.

Authors of relevant studies were also contacted to request details of ongoing or unpublished investigations.

One author was responsible for hand searching and identification of eligible studies, whilst the other three authors examined the electronic search results and identified potentially eligible studies.

All languages were considered.

4. Did the review's authors do enough to assess the quality of the included studies?

Yes.

The review stated that the four authors evaluated study quality and extracted data.

Authors of the included trials were contacted to provide missing data and information regarding the trial.

Individual patient data was sought to enable comparisons of mean values across studies.

To perform intention to treat analysis, all data extracted reflected the original allocation groups where possible.

Losses to follow up were identified where possible.

For the majority of trials the authors estimated means and standard deviations from graphs presented without tabulated data in the trial reports.

The Authors used a modified method previously outlined by Schultz et al (1995) to assess the study quality. They assessed the adequacy of randomisation, adequacy of allocation concealment, completeness of outcome data and the level of masking.

The Authors also made comments on issues they identified regarding the study process. The Authors failed to mention what type of critical appraisal tool they used.

Sensitivity analysis, based on the Schultz et al (1995) score was performed to investigate the effects of study quality and the missing data. This allowed the analysis of more than one set of assumptions to investigate any discrepancies.

The authors looked at best and worst case scenarios. Best = none of the originally enrolled participants missing from the primary analysis in the treatment group had the negative outcome of interest whilst all those missing from the control group did. The reverse of this outcome was used as the worst case scenario.

The quality of the studies' methodology was assessed and considered fair to high. The randomisation procedure was not described in seven of the 9 studies.

5. If the results of the review have been combined, was it reasonable to do so?

Yes.

The results of the different injuries were combined. However, the different injury categories were analysed separately. The different categories separately analysed were tendon / ligament injury or DOMS. Considering the differing injury type it could be considered reasonable to do so.

In addition, subgroup analysis where appropriate data was available was considered of the following: injury entry grade or severity, type of injury/location, oxygen received , ATA, time, length of treatment course, type of comparative treatment, age (adults versus children), nature of activity undertaken

6. What are the overall results of the review?

Insufficient evidence from comparisons tested within randomised controlled trials to establish the effects of HBOT on ankle sprain or acute knee ligament injury.

The studies showing significant improvement:

- For ankle sprains, Borromeo (1997), reported a significant improvement on functional assessment in HBOT compared to control. However, the authors suggest that the scale has not been validated and therefore the results should be interpreted cautiously. Pain scores were also higher for the HBOT group, although there was no significant difference after the final treatment session. The mean scores were statistically significantly better in the HBOT group after 10 treatments, but not after 5 treatments, for grade II medial collateral injury (Soolsma, 1996). However, a number of features in this study remain unclear; the number of participants allocated to each arm are unknown.

- No evidence suggests that HBOT improves speed of recovery from DOMS treatments (Webster, 2002; Harrison, 2001; Mekjavic, 2000; Staples 1999b; Staples, 1999a).

- There was some evidence that in treating muscle soreness, HBOT may hinder recovery, as there was a statistical significance in pain scores at 48 hours (Harrison, 2001; Mekjavic, 2000; Staples, 1999b; Staples, 1999a). However, no statistical difference was shown at the end of treatment.

7. How precise are the results?

Different injury categories; tendon / ligament injury / DOMS, were analysed separately. The majority of the results displayed on the forest plots show cross the line of no effect. This would support that there was no significant difference between treatments. However, these results may be as a result of the sample size being too small to be confident where the true result lies.

Ankle function displayed 95%CI of (0.15 - 2.65) suggesting statistical significance. However, as previously stated the authors report that the scale has not been validated.

The results of subgroups for HBOT versus control for induced DOMS displays that the observed difference is not statistically significant, because from the majority of results the 95% CI do not cross the relative risk of 1. With only HBOT pain scores of statistical significance demonstrated at 48hrs and 72hrs.

8. Can the results be applied to the local population?

There was only a small number of studies with only one study for ankle sprain and one for acute knee ligament injury. It is difficult to draw conclusion from a small number of participants.

Two trials evaluated HBOT for soft tissue injury presenting within 72 hours of injury. There was no mention of subject age or gender. The other seven trials included unconditioned young adults, studies enrolling females only, males only and a mix of males and females.

Participants in the studies included in the review do not accurately reflect a population of conditioned male professional footballers. However, they would not be sufficiently different from our population to cause concern.

9. Were all important outcomes considered?

From the studies review the following outcomes were considered:

Primary outcomes:

- Proportion returning to pre-injury activity
- Time to reach full function following injury

- Persisting pain following injury

Secondary outcomes:

- Functional assessment scores
- Pain and swelling
- Strength
- Complications of therapy

Bennett et al, (2010) mentioned the following outcomes but failed to consider any in the final outcomes:

- Creatine Kinase has been previously studied in relation to muscle damage due to strenuous exercise. Two of the later studies (Babul, 2003; Germain, 2013; Harrison, 2001) include this in their outcomes.

Other outcomes mentioned but not considered in the review outcomes are:

- Serum malondialdehyde (This reactive species occurs naturally and is a marker for oxidative stress) (Babul, 2003)
- MRI (Babul, 2003., Harrison, 2001; Soolsma, 1996; Webster, 2002)
- Magnetic resonance spectroscopy (Webster, 2002)
- Ratio of figure of 8 to straight running ability (Soolsma, 1996)
- Transcutaneous oxygen measurement (Harrison 2001; Mekjavic, 2000)

From this, it might be suggested that Bennett et al, (2010) omitted some important outcome measures.

10. Are the benefits worth the harm and costs?

The recommendation is that HBOT is safe, although there needs to be further studies carried out to support its use. Nothing is mentioned in the paper regarding costs, therefore difficult to report on the cost effectiveness of HBOT.

A Summary of the Review of Bennet et al, (2010)

Following appraisal of the review by Bennett et al. (2010), using the CASP tool, it can be concluded that the review is of good methodological quality. CASP identified an unbiased inclusion / exclusion criteria and that the search was detailed, exhaustive and multifaceted. However, in agreement of our view the included studies were not of high methodological quality. The study by Babul (2003) was identified as higher in quality than the other studies; however, this was omitted from the review along with the Germain et al., (2003) study due to the lack of data. The review concluded that the use of HBOT for closed soft tissue injury and delayed onset muscle soreness cannot be justified from the findings.

HBOT as a Treatment for Fractures

This section describes a review of the literature to determine whether HBOT is a suitable intervention for the treatment of fractures.

Electronic searches of the following databases were undertaken:

- The Cochrane, Joint and Muscle Trauma Group Specialised Register (to September 2015)
- AMED (Allied & Complimentary Medicine. 1985 to September 2010)
- OVID MEDLINE (1946 to September Week 4)
- SPORTDiscus (1980 - present)
- Searched Reference lists of articles

Key words used:

Fractures, bone, fixation, fracture healing, non-union, delayed union Hyperbaric oxygenation, oxygen, hyperbaric, chamber, monoplace, multiplace, Randomised controlled trial, controlled clinical trial, controlled study, prospective study double blinded, single blinded.

All randomised and quasi-randomised controlled trials that compared HBOT with no HBOT (sham or no treatment) were included.

Patients with bone fracture, delayed, or non-union of bony fractures.

No restrictions on gender or age were made.

Any standard HBOT treatment regimen using pressures 1.5 ATA - 3 ATA for 30 minutes to 60 minute individual treatment periods for promoting fracture healing or delayed or non -union was accepted.

The search revealed no randomised controlled trials with appropriate outcomes to support the use of HBOT for bone fracture, delayed or non-union of bony fractures. 3 ongoing trials were identified registered trials in progress: One being a multi centred international non-blinded randomised trial: 'Hyperbaric Oxygen for Lower Limb Trauma' (HOLLT) study which includes patients with complex fracture of the lower leg following crush injury (Millar et al, 2015). The second, the 'Hyperbaric oxygen therapy in calcaneal intra-articular fractures: can it decrease the soft-tissue complication rate (HOCIF) trial. A randomised controlled trial (single centre) to include approximately 160 people (Knobe, 2011). Thirdly, 'Hyperbaric oxygen therapy in distal radius fractures: can it shorten recovery time and increase fracture healing? (HBOTRadius), to include approximately 100 patients (Knobe, 2011). A Cochrane review by Bennett et al, (2012) on promotion of fracture healing and treating fracture no union was also located.

The review by Bennett et al, (2012), failed to locate any randomised controlled trials that confirmed or refuted the use of HBOT in the treatment of non-union bony fractures and delayed bony healing. Of the 11 full text articles found and assessed for eligibility the review excluded 5 reviews as they contained no new data. Three RCTs were excluded as two did not report on fracture healing outcomes and one had been abandoned. The remaining three articles were the three registered trials in progress previously mentioned

A Summary of the review of HBOT as a Treatment for Fractures

Despite HBOT demonstrating potential benefits in animal studies, HBOT has failed to demonstrate its effect in the treatment of delayed bony healing and non-union of bony fractures in humans (Inoue et al, 2000; Wang et al, 2005). No evidence exists to support of refute the use of HBOT. Future evidence to support the use of HBOT may be identified in the 3 ongoing clinical trials.

Conclusion / Recommendations

There is an abundance of anecdotal evidence to support the use of HBOT. However, there remains a scarcity of detailed randomised controlled trials to support its use.

As previously described HBOT has guidelines and has been cleared for its safe use in a number of conditions with clear evidence of its use in decompression sickness and a small number of other conditions.

No accepted guidelines currently exist for DOMS, closed soft tissue injury, fracture healing or treating fracture non-union. Despite this, treatment effects identified in other condition provide some promise for the inclusion of these conditions in the use of HBOT.

Side effects of HBOT have been identified and are usually mild, but in some rare cases may be life threatening. However, by ensuring contraindications and precautions are identified and correct safety procedures are adhered to problems should not occur and the delivery of HBOT be considered as safe

Research to date has yet still to determine the beneficial physiological, biochemical and cellular effects achieved with HBOT. Staples et al, (1999) in the analysis of treatment effect for inflammation suggests the need to monitor biochemical markers to determine whether HBOT benefits are as a result of inflammatory reduction or as a result of the enhanced healing ability of the body.

Parameters for a number of indications have been suggested. However, in order to obtain the best clinical and cost effective results further work remains to be carried to determine best timings, indications and therapeutic protocols.

It has been suggested that the most beneficial results in previous studies looking at re-perfusion of ischemic muscle in burn therapy occurs when HBOT is initiated in the first 8 hours (Zamboni et al, 1993; Cianci & Sato, 1994). Many studies fail to administer HBOT early enough

to gain the most beneficial effect, especially in cases where reduction of inflammation and the pain associated with it is considered one of the primary outcomes

Future research should aim to include well conducted randomised controlled with larger and carefully selected sample sizes. More consideration should be given to the correct HBOT timing and number of treatments, to help determine the most effective dosage and at what stage of treatment.

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