Hyperbaric oxygen therapy (HBOT) for the prevention and treatment of osteoradionecrosis following radiotherapy of head and neck cancer

HBOT involves breathing pure oxygen under a pressure of greater than one atmosphere absolute and has been proposed for preventing and treating various conditions where there is inadequate supply of oxygen to the tissues.

Health technology description

Hyperbaric oxygen therapy (HBOT) involves inhalation of 100% oxygen under a pressure of greater than one atmosphere absolute (ATA). It was initially used to treat decompression illness in divers but has subsequently been applied to treat other conditions including necrosis of the bone caused by radiation therapy (osteoradionecrosis). The high pressure increases the amount of oxygen being circulated within the body, which is believed to have various effects including the promotion of vascularisation (growth of blood vessels). Patients inhale pressurised oxygen either through a hood or mask in a multiplace hyperbaric chamber (see picture on the right), or through an oxygen-filled monoplace chamber in which the patient lies (see picture overleaf).

The most widely used protocol for HBOT in the prevention and treatment of osteoradionecrosis is a protocol that was initially developed by Marx and colleagues in the 1980s (the ‘Marx protocol’). It consists of 20 HBOT sessions prior to a surgical procedure being carried out in a previously irradiated area and 10 sessions after the procedure. Each HBOT session (sometimes referred to as a ‘dive’) involves breathing pure oxygen at 2.4 ATA for 90 minutes. The protocol is frequently modified in practice to suit local facilities and circumstances. Variations exist in the total number of sessions (30 - 60), pressure used (2.0 - 2.5 ATA), length of each session (60 - 120 minutes), frequency (once or twice a day), adoption of a 5-minute reprieve in every 30-minute interval for preventing oxygen toxicity and continued administration of pure oxygen during the decompression period.

The latest guideline issued by the Scottish Intercollegiate Guideline Network on diagnosis and management of head and neck cancer makes a grade C recommendation that hyperbaric oxygen facilities should be available for selected patients while highlighting the lack of good quality evidence.

Key points

- Limited evidence indicates HBOT is effective in preventing osteoradionecrosis associated with tooth extraction.
- There is a lack of evidence regarding the effect of HBOT on tooth implants and associated osteoradionecrosis.
- A trial of high quality has shown that HBOT alone is not effective in treating osteoradionecrosis of the mandible (jaw bone) compared to placebo.
- Limited evidence suggests HBOT may be effective in promoting the healing of osteoradionecrosis of the mandible following surgical interventions.
- Differences in treatment protocols may limit the applicability of evidence from the literature to clinical practice.
- The cost effectiveness of HBOT in the prevention and management of osteoradionecrosis has not been assessed within the UK context.

continued overleaf
Epidemiology

Approximately 1,000 patients are registered in Scotland each year with new cancers of the head and neck, the commonest of which includes cancers of the oral cavity, pharynx and larynx. Radiation therapy is one of the main treatment modalities for these cancers. Despite being targeted at cancerous cells, radiation therapy inevitably causes damage to surrounding normal tissues. Whilst acute injury generally resolves following the completion of the radiotherapy, late tissue injury such as osteoradionecrosis may develop months or years after radiation therapy. Osteoradionecrosis may occur spontaneously or be induced by subsequent injury in the irradiated area. It can be serious, debilitating and difficult to treat. The incidence of osteoradionecrosis in the head and neck region ranges from 1 - 37.5%, with the range of 5 - 15% being most commonly reported. Osteoradionecrosis of the mandible (jaw bone) is the commonest site in patients who receive radiotherapy for head and neck cancer because of the relatively poor vascularisation in this area. It also occurs due to injuries to the mandible caused by dental infection and procedures such as tooth extraction or implant subsequent to the radiation therapy.

Clinical effectiveness

Two Cochrane systematic reviews cover the use of HBOT in the prevention of osteoradionecrosis. A review from 2002 on HBOT for patients who required dental implants in an irradiated area did not identify any relevant randomised controlled trials (RCTs). Another broad review of HBOT for late radiation tissue injury published in 2005 included six RCTs, two of which are relevant to this Evidence Note. One of the RCTs concerns prevention of osteoradionecrosis and another relates to its treatment. The preventive trial evaluated HBOT in 74 patients who needed tooth extraction in an irradiated area. Significantly fewer patients treated with HBOT (90 minutes at 2.4 ATA daily, 5-6 days a week, 20 sessions before and 10 sessions after tooth removal) developed osteoradionecrosis (tooth socket wounds that failed to heal) six months after the dental procedure compared to those treated with perioperative penicillin (5% vs 30%, P=0.005).

The other trial involved patients who had already developed osteoradionecrosis. It compared HBOT (using the same treatment protocol as above) to control (not specified) in 104 patients who required hemimandibular jaw reconstruction due to osteoradionecrosis. Several criteria including achievement of bone continuity and maintenance of bone form for 18 months were utilised to define treatment success. The success rate was significantly higher in the HBOT group compared to the control group (92% vs 65%, P=0.001). There were methodological weaknesses among the above trials, including unclear methods of randomising patients and lack of blinding (the doctors who treated/assessed the patients knew whether the patient received HBOT). An additional small RCT was identified but was not included in the Cochrane review as quantitative outcomes were not provided. It reported ‘significant improvement for healing process’ for HBOT at 2 ATA compared to pure oxygen given at 1.2 ATA in 12 patients with mandibular osteoradionecrosis.

One relevant RCT has been published since the above reviews. This double-blind trial compared HBOT (90 minutes at 2.4 ATA twice daily, 5 days a week, 30 - 40 sessions) to placebo (a mixed gas of 9% oxygen and 91% nitrogen instead of pure oxygen) for the treatment of overt mandibular osteoradionecrosis in 68 patients. The trial was terminated early according to results of its interim analysis as fewer patients in the HBOT group had recovered at one year compared to the placebo group (19% vs 32%, P=0.23). Approximately 80% of patients in this trial had no a priori need for surgery at study enrolment. As any subsequent need for surgery during the trial was defined as a treatment failure, the reported rates of recovery primarily reflect the effect of HBOT (or placebo) alone and are noticeably lower than the success rates in the aforementioned trial, in which the treatment outcome represents the effect of HBOT in conjunction with surgery. Potential differences in conjunctive surgical procedures add difficulty in comparing results between trials. The generalisability of trial results is further complicated by varied modifications to the Marx protocol in clinical practice.

There exist several other systematic reviews and health technology assessment (HTA) reports, some of which include observational studies in addition to RCTs. No relevant RCTs other than those described above were identified for this Evidence Note.
Safety

Only one of the RCTs reported adverse events.\(^{10}\) Three percent of patients in the HBOT group experienced otic barotraumas (injuries to the middle ear due to high pressure) and 6\% had at least one session discontinued due to complications. Other adverse effects of HBOT include myopia (short eye-sighted) which is generally reversible, and rare complications such as oxygen seizures and pulmonary barotraumas.\(^{12}\) Very rare but serious accidents in hyperbaric facilities involving fire or pressure highlight the importance of stringent safety measures.\(^{13}\)

Economic implications

There are several hyperbaric oxygen chambers in Scotland.\(^{17}\) Some are used exclusively for treating decompression illness while others offer treatment of other conditions. The availability of elective HBOT for the prevention and treatment of osteoradionecrosis depends on funding arrangement and the level of medical and technical support. The majority of elective HBOT within NHSScotland is currently carried out in the Hyperbaric Medicine Unit at the Aberdeen Royal Infirmary and the Wolfson Hyperbaric Medicine Unit at Ninewells Hospital in Dundee. The Aberdeen unit has a multiplace chamber and is currently funded by the National Services Division (NSD) of NHS National Services Scotland as a national service for the treatment of diving related illness. Elective HBOT for patients within NHSScotland has proved feasible within this funding arrangement. The Wolfson Hyperbaric Medicine Unit at Ninewells Hospital in Dundee has three monoplace chambers and is currently funded by the Barclay Foundation (Personal communication, Dr Petra Kliempt, 28 November 2006). These chambers are not registered for treating decompression illness for NHS patients, but can be used for treating NHS patients (mainly from Ninewells Hospital) for other conditions.

As NSD fund the Hyperbaric Medicine unit at Aberdeen to provide 24 hour intensive therapy unit (ITU) level care for diving-related injuries, staff costs for elective HBOT for the prevention or treatment of osteoradionecrosis are covered under this arrangement. There is a fixed charge of £32 per 90-minute session at 2.2 ATA (this cost also includes the administration of pure oxygen continued during an additional 30-minute decompression period until the pressure is reduced linearly to 1.3 ATA), corresponding to £960 - £1280 for 30 - 40 sessions for compressed gas and other consumables. This is invoiced to the referring Board. Any transport or overnight accommodation costs are the responsibility of the referring board. Inter-Board service level agreements should be assessed for inpatient and outpatient costs.

The cost per HBOT session at Ninewells Hospital was estimated at £30 - £41,\(^{18}\) or £900 - £1640 for 30 - 40 sessions (60 minutes, 2.0 ATA) in 2004. These estimates include costs related to compressed gases, consumables and staff costs, and are based on assumed patient throughputs of 1,320 - 1,410 sessions per hyperbaric unit per year with single monoplace chamber (e.g. 30 sessions per week, per monoplace chamber over 44 - 47 weeks; estimated cost per session increases as patient throughput per year decreases). The arrangement for other costs such as hospital bed (or alternative accommodation), outpatient visits and investigations, and patient transport should be agreed between the referring board and Ninewells Hospital.

A published cost-effectiveness analysis in Canada based on a retrospective study of 21 patients and a hypothetical control group using data from literature concluded that HBOT is cost saving compared to usual care in the management of osteoradionecrosis.\(^{19}\) Another HTA report estimated an incremental cost per case of osteoradionecrosis avoided to be Au$28,480 (Australian) for HBOT compared to penicillin.\(^{12}\) The analysis however did not take into account the costs for the management of osteoradionecrosis that were avoided. A robust economic evaluation adopting a NHS perspective is lacking and therefore the cost-effectiveness of HBOT to NHSScotland is unknown.

Further information

- Aberdeen Royal Infirmary Hyperbaric Medicine Unit, Aberdeen:
  http://www.hyperchamber.com/index.htm
- Wolfson Hyperbaric Medicine Unit, Dundee:
  http://www.dundee.ac.uk/surgery/hyperbaric/welcome.htm

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References