ECHM Workshop report

Controversial issues in hyperbaric oxygen therapy: a European Committee for Hyperbaric Medicine Workshop

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Hyperbaric oxygen therapy, bone necrosis, hypoxia, brain injury, autism, medical conditions and problems, clinical audit

Abstract

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Every few years, the European Committee for Hyperbaric Medicine (ECHM) publishes its recommendations concerning the clinical indications for hyperbaric oxygen therapy (HBOT). The last recommendations were issued during the 7th European Consensus Conference on Hyperbaric Medicine in 2004. Since then, several publications have reported on the use of HBOT in some indications in which it has not yet been recommended routinely, namely aseptic bone necrosis, global brain ischaemia and autism. Patients or their families push physicians and staff of hyperbaric facilities to use hyperbaric treatment regardless of the quality of the scientific evidence. Therefore, the ECHM Workshop "*Controversial issues in hyperbaric oxygen therapy*" was convened as a satellite meeting of the 2010 European Underwater and Baromedical Society Annual Scientific Meeting in Istanbul, Turkey in 2010. For each topic, a set procedure was used: first came a general report by specialists in the topic, incorporating a review of current pathophysiological, experimental and clinical evidence. Then, there were reports from hyperbaric facilities that had gained clinical experience in that condition, followed by a general discussion with specialists present in the audience. Finally, statements regarding each topic were proposed and voted on by the audience and these were presented to the ECHM Executive Board for consideration and possible approval. In conclusion, the use of HBOT in femoral head necrosis will be proposed during the next ECHM Consensus Conference to become an 'accepted' indication; whilst the use of HBOT in global brain ischaemia and autism should retain its current ECHM recommendations, that it should be 'optional' and 'non-accepted' respectively.

Introduction

The European Committee for Hyperbaric Medicine (ECHM) workshop on "*Controversial issues in HBO*" was held as a satellite meeting of the 2010 EUBS Annual Scientific Meeting in Istanbul, Turkey. It focused on three controversial conditions that are not yet accepted as indications for hyperbaric oxygen therapy (HBOT) on the ECHM list:[1]

- aseptic bone necrosis;
- global brain ischemia;
- autism.

For each topic, there are several publications available on the use of HBOT and there are repeated requests from patients or their families to physicians and staff of hyperbaric facilities to use HBOT either in standard or experimental mode to treat these conditions. Therefore, in order to recognise the potential inclusion of these indications in the ECHM recommendations for use of HBOT,[1] general introductory reports were presented by specialists in each field with a review of current pathophysiological, experimental and clinical evidence. These presentations were followed by short communications from representatives of HBOT facilities having clinical experience in that condition. These were followed by general discussion to which specialists present in the audience contributed. Based on all presentations, reports on personal experiences and general discussion, the final statements regarding each topic were proposed and voted on by the audience. These statements were then presented to the ECHM Executive Board for approval. Therefore, the final conclusions from this workshop reflect the current position of the ECHM with regard to HBOT in these three conditions.

Aseptic bone necrosis

L Ditri (Italy), J Desola (Spain), J Von Reumont (Germany)

- Magnetic resonance imaging (MRI) is the best technique at present for diagnosing aseptic bone necrosis (ABN), particularly in the early stages of its pathology when plain radiography is negative for bone damage or collapse.
- Grading of ABN is useful for determining whether HBOT is indicated and for monitoring its effectiveness. The Steinberg classification system, which is based on MRI imaging, should be used in preference to other grading systems.[2]
- The clinical goal sought by surgical and clinical specialties is delay or avoidance of the need for hip arthroplasty.
- Use of HBOT in ABN is based on its physiological

effects: increasing oxygen availability to cells, enhancing osteoblast and osteoclast function, reducing oedema (by oxygen-osmotic pump and vasoconstriction mechanisms) and thereby reducing the intraosseous pressure. This brings about an improvement in venous drainage and microcirculation, mobilisation of stem/progenitor cells from the bone marrow by a nitric oxide-dependent mechanism and stimulation of neovascularisation for healing.
- HBOT appears to achieve significant beneficial results only in stage 1 or 2 of the Steinberg classification, before the collapse of the articular surface of the bone, so early diagnosis of ABN is mandatory.

Based on a literature review[3–7] and on the personal experience of experts, if HBOT is considered for ABN, then the number of HBOT sessions should be about 60–80 in no more than four consecutive months, at a pressure of 243–254 kPa (2.4-2.5 bar) for a time of 90 minutes' oxygen (O_2) breathing. This should be combined with the use of crutches to ensure complete non-weight bearing during the entire treatment course. In particular, the recent publication of a double-blind, controlled randomised trial (RCT) raises the level of clinical evidence for HBOT in ABN to level B ("*double-blind controlled, randomised studies, but with methodological flaws; studies with only small samples, or only a single study*").[7,8] Based on this literature review, Ditri proposed that ABN be included in the ECHM list of recommended indications for HBOT.

Three short reports were then presented on their personal clinical experience by Desola, Ditri and Welslau/von Reumont. Ditri (unpublished observations) reported that in 329 patients with mild to moderate ABN of the femoral head, femoral condyle and other sites (stage 1 or 2 in the MRI Steinberg classification) treated with long-term HBOT (40–100 HBOT sessions at 253 kPa (2.5 Ata), in conjunction with conventional non-surgical therapy (physical therapy, crutches, osteointegration, pain control) full recovery or significant improvement was observed in almost 70% of patients, while deterioration or lack of any change was observed in 30% of cases. Based on this observational and uncontrolled study, the protocol for a prospective multicentre research project has been prepared and is now ready for implementation.

Welslau and von Reumont (unpublished data) reported on an ongoing, prospective, uncontrolled study on HBOT in ABN involving the knee or talus. 333 patients with MRI-verified diagnosis (with ARCO classification) have received HBOT (from 6 to 62 HBOT sessions at 253 kPa) in conjunction with standard conservative therapy. In this group, out of 269 patients with ABN of the knee (ARCO grades varying from 1 to 4), 91.5% were symptom free or had only mild discomfort following HBOT, whilst 8.5% continued to deteriorate or had no change in clinical status.

The final outcome appeared to vary from centre to centre and country to country. The process of bone healing is slow, so one of the possible explanations for different outcomes is the number of HBOT sessions given. In all cases, MRI should be used before and after HBOT treatment to monitor the result of therapy.

After the general discussion, the audience was split fairly evenly between those who supported the inclusion of ABN on the ECHM list and those wishing to wait until more clinical data had been published.

Global brain ischaemia

B Ratzenhofer (Austria), D Mathieu (France), J Desola (Spain)

Cerebral metabolic rate is about 4 ml O_2 $100g^{-1}$ min^{-1}, with approximately half spent on maintenance of synaptic activity and half on maintenance of basal cellular function, such as protein/neurotransmitter synthesis, trans-membrane ionic gradients, anabolic enzyme reactions and Na^+/K^+ pump activity.

Over the past 30 years, it has been established that:
- there is a linear relationship between local cerebral blood flow (CBF) and brain tissue pH over a PO_2 range from 20–400 mmHg;
- reduction of PO_2 causes a decrease of local pH leading to vasodilatation and increased CBF;
- after an acute cerebral hypoxic episode, areas of heterogeneous perfusion remain, leading to chronic and varying degrees of O_2-deprivation (the so-called 'penumbra' in stroke, for example).[9]

Several thresholds for cerebral ischaemia are evident:
- at 50 ml $100g^{-1}$ min^{-1} neuronal function is normal;
- at 50–30 ml $100g^{-1}$ min^{-1} inhibition of protein synthesis, selective gene expression, neuronal loss and lactic acid generation start;
- at < 30 ml 100 g^{-1} min^{-1} there is glutamate release, acidosis and ATP decline;
- at < 20 ml 100 g^{-1} min^{-1} infarction commences;
- at < 10 ml 100 g^{-1} min^{-1} K^+/Ca^{++} homeostasis is disrupted.

The heterogeneity of the brain in terms of circulation and metabolism is a challenge in the evaluation of the effects of HBOT. The ischaemic penumbra, the region where CBF is insufficient to maintain normal function, but just enough to maintain structural integrity, is the therapeutic target for HBOT.

The potential mechanisms of neuroprotection by HBOT include:
- increased oxygen delivery to neurons;
- stimulation of apoptotic inhibitors and free radical scavengers;

- inhibition of leukocyte adhesion through inhibition of ICAM-1;
- decreased breakdown of the blood-brain barrier;
- decreased oedema through oxygen-mediated vasoconstriction;
- stimulation of angiogenesis.[10]

Since the previous ECHM Consensus Conference in 2004, two new publications concerning global cerebral ischaemia in humans have appeared and were reviewed.[11,12]

Clinical experience was then presented by Desola and Mathieu. Desola (unpublished observations) reported that 34 previously healthy patients in coma (with one exception of a conscious patient with cortical blindness) after acute anoxic brain injury were treated with HBOT (60 min 100% O_2 at 233–283 kPa, once daily up to a median of 40 sessions, range 20–60), with a latency of 12 days to two months. In all cases, HBOT was started after patients failed to respond to standard care. Regardless of severity, improvement was observed in all patients, 28 with complete and six with partial recovery. Delay to HBOT treatment also did not appear to influence the final outcome.

Mathieu (unpublished observations) reported that, in a group of 305 patients after near-hanging, the following prognostic factors were found to be statistically associated with poor outcome: no lid reflex; cardiac arrest on site; coma > III or GCS <= 5, no light reflex and no HBOT.

During general discussion, the point was raised that combined hypothermia and HBOT therapy should be investigated for clinical efficacy. It was concluded that treatment with HBOT may possibly reduce mortality and neurological sequelae in term neonates with hypoxic-ischaemic encephalopathy. Despite widely differing study designs and clinical reports, the data suggest a beneficial effect. However, the optimal HBOT dosage and onset of treatment are yet to be defined. Because of the poor quality of reporting, a high-quality RCT is needed to investigate these findings.

After the general discussion, a majority of the audience voted for leaving the current recommendation for use of HBOT as it is, which is 'optional', in post-anoxic encephalopathy.[1]

Autism

N Motavalli (Turkey), J Schmutz (Switzerland)

- Studies on the pathogenesis of autism are far from claiming a single intervention method as a 'cure' for the disorder.
- Treatment approaches should focus on enhancing socio-emotional and communicative abilities as well as self-help skills in this group.
- The professionals should inform parents about the lifelong nature of the disorder and importance of appropriate early education programmes.

Schmutz presented a literature review of current evidence concerning HBOT use in autism.[13–15] It was concluded that some studies showed efficacy of HBOT in autism, but there were serious design limitations and a possibility that there was a strong influence not by HBOT itself but rather by associated learning and care procedures.

During general discussion, the majority of workshop participants confirmed that they had received requests from families for HBOT in the treatment of autistic children. With isolated exceptions, these requests were generally declined. However, the growing practice of 'mild hyperbaric therapy' (conducted in inflatable chambers with low pressures with air, installed in family homes) was recognised. This has been addressed in position statements by the Undersea and Hyperbaric Medical Society and the Australia and New Zealand Hyperbaric Medicine Group.[16,17]

The workshop confirmed that autism is not accepted as an indication for HBOT, as there is insufficient evidence currently. HBOT should only be used in autism within the framework of an ethically approved clinical trial. Use on compassionate grounds in individual cases should only occur if there is believed to be an acceptable scientific rationale, if the patient/parents, referral physician(s) and third party payer (if any) have been extensively informed about the potential risks and questionable benefit, and if treatment is at no cost to the patient.

Conclusions

- There is a good rationale for HBOT in aseptic bone necrosis, based on pathophysiological mechanisms. The personal experience of hyperbaric medicine specialists and cumulative clinical data confirm that HBOT can improve clinical outcome in Steinberg stage 1 or 2 cases. Therefore, approval for the use of HBOT in femoral head necrosis should be proposed during the next ECHM Consensus Conference as an 'accepted indication'.
- There is a good rationale for using HBOT in global brain ischaemia based on pathophysiological mechanisms. However, since the last ECHM Consensus Conference there have been only limited clinical data published. Therefore, there is no reason to change the current status of the ECHM recommendation, which is 'optional'.[1]
- Currently there is no clear rationale for HBOT in autism based on clinically proven pathophysiological mechanisms. The few studies on the use of pressurised environments (not always compatible with the definition of 'hyperbaric oxygen therapy') for autism have serious methodological limitations. Therefore, autism should remain as a non-accepted indication for HBOT. HBOT should be used only within the framework of an ethically approved clinical trial. Treatment of individual patients may occasionally be acceptable on compassionate grounds only with the agreement of all parties after extensive informed discussion and at no cost to the patient.

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Aseptic bone necrosis

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