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Review of appropriateness of MSAC consideration and prioritisation of evidence in relation to Hyperbaric Oxygen Therapy

Request

The Medical Services Advisory Committee has undertaken a Review of Interim Funded Service: Hyperbaric Oxygen Therapy (HBOT) for the Treatment of Chronic Non-Diabetic Wounds and Non-Neurological Soft Tissue Radiation Injuries. NHMRC was requested by the Department of Health and Ageing to provide a view of the appropriateness of MSAC's consideration and prioritisation of the available evidence.

Materials provided

The Office of NHMRC (ONHMRC) was provided with two studies: 'Hyperbaric Oxygen Reduced Size of Chronic Leg Ulcers: A Randomized Double-Blind Study' (Hammarlund and Sundberg, *Plastic and Reconstructive Surgery*, April 1994) and the ANZ Hyperbaric Medicine Group Australasian Wound Study (specifically 'The outcome of chronic wounds following hyperbaric oxygen therapy: a prospective cohort study – the sixth year report', Hawkins and Bennett) in draft form.

It is noted that the submission to MSAC of 2 August 2012 by the Australian Hospitals Association, the ANZ Hyperbaric Medicine Group and the AMA describes the latter study as "not yet complete—the final patients have been enrolled and 12 month outcome data will be available after March 2013" (p3). ONHMRC was also provided with the first year interim report of the Australasian Wound Study, which sets out the Study methodology in some detail (Hawkins GC, Bennett MH, van der Hulst A. The outcome of chronic wounds following hyperbaric oxygen therapy: a prospective cohort study—the first year interim report. *Diving and Hyperbaric Medicine*. 2006; 36:94-98).

For background, ONHMRC was also given:

- the publicly available information in relation to MSAC's Review of Interim Funded Service, including the public summary, assessment report, dissenting report and short minutes of the reconsideration
- the applicant's letter with background, July 2012
- the applicant's submission to MSAC for reconsideration, August 2012
- minutes of MSAC meeting at which HBOT was reconsidered, August 2012
- further applicant submission, September 2012
- applicant's response to the MSAC August minutes, September 2012

The review has been undertaken by one of ONHMRC's Executive Knowledge and Development Officers, with expertise in evidence assessment and guideline development.

Description of studies

Hammarlund and Sundberg's quasi-randomised controlled trial consisted of 16 otherwise healthy patients, each presenting with at least one non-diabetic, chronic leg ulcer of more than one year's duration. Exclusion criteria were also applied (smoking, chronic disease such as diabetes mellitus, or large vessel disease). Patients were divided into two groups, according to age (< 50 years and >50 but <75 years) and randomly allocated to either the study group or the control using envelopes (but these envelopes are not described as being sequentially numbered). Eight patients were given air treatment under hyperbaric conditions and eight patients given oxygen treatment under hyperbaric conditions.

Each patient was treated in a pressure chamber with a double mask breathing system, breathing either oxygen or air for 90 minutes, 5 days a week for a total of 30 treatments at 2.5 ATA. The gas supply was blinded for all persons involved.

All patients completed all 30 treatments. Only one wound from each patient was used, with measurements taken 2 weeks before hyperbaric treatment was commenced and then 2, 4, 6, and 18 weeks following commencement.

It was reported that the mean decrease of the wound areas at weeks 2, 4 and 6 in the oxygen group were 6.6 per cent (SD± 14), 22 per cent (SD±13), and 35.7 per cent (SD± 17), respectively, and in the air group, 2.8 per cent (SD± 11), 3.7 per cent (SD± 11) and 2.7 per cent (SD± 11), giving a *p* value less than 0.05 at week 4, and a *p* value less than 0.001 at week 6 between the groups.

The authors concluded that the study showed a significant effect on the wound healing of nonatherosclerotic, nondiabetic chronic leg ulcers. Hence HBOT might be used as a valuable adjunct to traditional therapy when conventional therapies have failed.

The ANZHMG Wound Care study involved 441 patients, who presented at ten of the fourteen hyperbaric facilities in Australia and New Zealand. All patients presenting for assessment of a chronic wound (greater than three months' duration) were eligible for inclusion in the study, regardless of decisions on therapy or suitability for hyperbaric oxygen treatment. Exclusion criteria were applied, including wounds of less than three months duration, wounds that had surgical intervention within the past three months and wounds associated with exposure to radiation.

Patients were divided into groups according to the type of wound being treated: diabetic, peripheral vascular disease, venous disease and miscellaneous. Assessments on a reference wound were performed at the end of the course of HBOT and at one, six and 12 months post hyperbaric treatment. No approach was made to standardise the approach to therapy for the patients enrolled in the study, either for the general approach to wound care or the HBOT schedule.

In total, 355 patients received five or more hyperbaric treatments, with the number of treatments ranging from 6 to 70, with a mean of 28.2. The study classifies patients receiving less than five hyperbaric treatments as "No HBOT". As there is only a relatively small number of these patients, the study limits its analysis of this category.

The degree of healing was assessed against a six-point scale. Categories 1-4 (no healing or some healing) were recorded as a 'bad outcome' while categories 5 and 6 (healed) were recorded as a 'good outcome'. Only patients with a 'good outcome' were considered successful.

At the study's six year mark, the percentages of patients with a 'good outcome' at each assessment period was 43.9 per cent, 54.2 per cent, 68 per cent and 80.4 per cent respectively.

The authors conclude (in the draft study) that HBOT has a significant impact in the improvement of chronic indolent wounds with the improvement continuing out to at least 12 months after treatment regardless of the aetiology of the wound.

Findings

It is noted that both sources of evidence are weak and an appropriately powered randomised controlled trial would provide a stronger evidence base. The quasi-randomised trial (Hammarlund and Sundberg) is very small (16 patients) and achieved randomisation through envelopes selected at random rather than sequentially. Both sequence generation and allocation concealment are inadequate for full randomisation.

While the ANZHMG Wound Care Study attempts to collect additional information by following a cohort of patients presenting for HBOT, the absence of a control group means it is unable to contribute to the question of comparative effectiveness.

MSAC has appropriately considered both studies and given each the appropriate weight, in ultimately prioritising the quasi-randomised controlled trial above the prospective cohort study. This is consistent with the way ONHMRC evaluates evidence, for example in the development of clinical practice guidelines.

Generally speaking, NHMRC considers that individually, well designed and conducted randomised controlled trials are the best source of evidence for effects of interventions because randomisation minimises biases that may occur when individuals are allocated in an open fashion to the intervention or control groups. It also minimises or eliminates confounding due to an unequal distribution between groups, of factors that influence the clinical outcome under study.

There are a number of potential problems with nonrandomised studies (which include comparative studies with concurrent or historical control groups, cohort studies and case-control studies). These include:

- Noncomparability of groups due to purposive selection of subjects to receive the intervention;
- Different cointerventions and other medical management being received by the groups being compared; and
- Different methods of outcome measurements being used in each of the groups being compared.

Of these the first is probably the most important and insurmountable within nonrandomised studies; for example, selection bias where those allocated to receive the new treatment or intervention are chosen (consciously or unconsciously) because they are expected to do well. There is also the 'healthy cohort effect' in which individuals who are inherently healthier, or more compliant, self-select to the intervention of interest (eg by choosing to take hormone replacement therapy after menopause) (Barret-Connor 1991).

The use of historical controls (a group who received what was, in the past, standard care) to compare with a group who have more recently received the new treatment is also problematic. The new treatment may have been offered selectively to patients in whom it is likely to succeed. Also, a number of other factors (such as cointerventions, medical management, outcome determination) in addition to the introduction of the new treatment, may explain the observed differences between the two groups.

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