

From Dr Ken Thistlethwaite
Medical Director, Wesley Centre for Hyperbaric Medicine, Auchenflower Brisbane.
7/11/2012.

Standing Committee on Finance and Public Administration

Inquiry into Medicare funding for Hyperbaric Oxygen Treatment.

The Wesley Centre for Hyperbaric Medicine is a fully comprehensive service, treating diving emergencies, carbon monoxide poisoning and necrotising infections including gas gangrene. Approximately 40% of our patients fall into the 13015 item number and include treatments of non-diabetic leg ulcers (biggest group), flaps, grafts, crush injuries and support for surgical procedures where the surgical wounds are failing due to poor tissue perfusion. Hyperbaric Medicine is a sub-specialty of the Australian and New Zealand College of Anaesthesia. There is ongoing peer review and every three years the international body (Undersea and Hyperbaric Medicine Service - UHMS) publish the updated guidelines and current evidence base for appropriate use of the technology. It is unfortunate that in the past, units that are not comprehensive hyperbaric medical units have been able to "practice" and that an underserved reputation for being an "alternative" therapy established.

The many thousands of patients that we have healed after failing "standard" wound care has been verified by the results of the longitudinal study at the Prince of Wales Hospital. This study confirmed that in excess of 80% of these patients were healed at 1 year post presentation. The results from this study although very encouraging re-inforced the need to conduct a properly constructed, blinded, randomised control trial. This trial was designed and put together over a year in a co-operative arrangement with the Federal Government funded, national, Wound Management Innovation CRC (<http://www.woundcrc.com/>). This is a double blinded, randomised, control trial involving "gold standard" wound care for 4 weeks with failure to reduce the surface area of the wound by 50% being the trigger for randomisation into a hyperbaric oxygen treatment arm or a sham arm (see attached appendix). This trial is very important not only to us but the world wide community. It appears unbelievable that the federal government acknowledges the requirement for study to be completed and funds it; yet withdraws the item number associated with this research, based on lack of evidence. The point being that lack of evidence of effect is not evidence of lack of effect. Having come this far, why compromise the results of this study by initiating premature change? Why fund the study if you do not intend to see it through?

Medicare's own financial data clearly displays the benefit of appropriate use of hyperbaric oxygen therapy in treatment of these wounds. Our therapy has always been used as adjunctive therapy after conventional therapy has failed. Medicare data shows that healing rates are drastically reduced in the 3-6 month range with conventional therapy alone (9% for this period of time). If hyperbaric oxygen therapy is added to the regime this figure is increased to nearly 60% and if the Prince of Wales data is to be believed, would be expected to climb to over 80% at one year. Our trial answers the lack of evidence question but will cease if the viability of the unit conducting the study is threatened. The impact of this decision to withdraw funding results in the immediate loss of 38% of the business income (the majority of this being private Health Funds and Veterans benefits which depend on the existence of a Medicare benefit). The decision will mean job losses at our facility. My personal belief is that this decision will cause the termination of the study without the question of evidence of effect ever being answered.

Wound care in general is very poorly dealt with in primary health care. Medical practitioners receive very little training in wound care and the cost and range of dressings is prohibitive for a lot of general practice. Hyperbaric oxygen facilities provide a source of expertise in the area of wound care due to their involvement in "13015" presentations. Our extensive involvement in this area allows us to stock the necessary range of dressings and provide the time required for investigation, debridement, dressings and care plans for the primary care community. I personally provide wound care expertise to the medical community through hospital, local and RACGP education presentations. Wound clinics in the private setting are limited and we fill a niche role that is not recognised. Our clinical indicators for the period January – June 2012 reveal that 77% of the wounds that we treated had significant healing, 9% partial healing and 14% unlikely to heal. Our "removal" from the health care system will only shift the burden of care to infectious disease specialists, plastic surgeons and vascular surgeons and their associated hospitals. Up until now we have provided a cost effective screening facility which will now be transferred to these "specialty" areas. This will come with a significant increase in cost burden and waiting times for a group of people often vulnerable to financial cost, travel and pain management.

There are also the rare ischaemic "13015" presentations for which we provide invaluable primary care. Recent examples include the treatment of a 14 year old girl with a gas forming infection of the foot due to a horse float crush injury and frost bite in a 35 year old lady after trekking in Nepal. Both of these examples were advised to have below knee and forefoot amputations. Both of these young ladies avoided amputation and a lifetime of significant costs to the health purse.

What do we (The Wesley Centre for Hyperbaric Medicine) stand to lose.

- The ability to treat wounds that have failed conservative therapy
- The ability to demonstrate effectiveness or lack of effect through a federally funded RCT trial
- Our expertise in wound care
- Our Jobs

What does the Federal Government stand to lose?

- Their current investment to date, in the above mentioned trial.
- The significant savings in wound care management demonstrated by their own figures.
- Community expertise in wound care.
- Money associated with the obvious increased admission rate to deal with presentations that could have been dealt with in the community.

Regards

Dr Ken Thistlethwaite BSc(Hons), MBBS, FRACGP (JCCA).

Appendix 1

Summary of Venous Ulcer Randomised controlled trial

The effectiveness of hyperbaric oxygen therapy (HBOT) for healing chronic venous leg ulcers: A randomised double blind, placebo-controlled trial. Clinical trials Registry No: ACTRN12611000505909

Protocol No: WMI CRC 3-0 Version 2.0 dated 15/4/2011

Principal Clinical Investigator Dr Ken Thistlethwaite / QUT Investigator Prof Helen Edwards

Queensland University of Technology University Human Research Ethics Committee (EC00171) HREC 1000001172

Uniting Care Health Human Research Ethics Committee (EC00374) HREC 1102

Lead Investigator at Royal Hobart Hospital – Dr David Cooper

Tasmania Health & Medical Human Research Ethics Committee (EC00337) Reference No. H12288

There is commitment to the trial at Prince of Wales Hospital in Sydney and Fremantle Hospital in Perth.

ACTR Number:	ACTRN12611000505909
Trial Status:	Registered
Date Submitted:	1/05/2011
Date Registered:	16/05/2011
Date Last Updated:	16/05/2011
Registration Type:	Prospective registered

The design, conduct and reporting of this trial is undertaken in compliance with the Protocol, the Australian Therapeutic Goods Administration (TGA) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, DSEB July 2000) and the TGA Australian Regulatory Guidelines for Medical Devices – Version 1.0 April 2010: Part 3 – Post-market.

Funding: Name of Grant / Sponsor Dept. Innovation, Industry, Science and Research CRC Program (Wound Management Innovation CRC, Level 2, 8 Carraway Street, Kelvin Grove QLD 4059)

Trial Budget: \$1,616,712

Funding: WCHM = \$150,000 WMI CRC = \$191,700

In kind funding will be provided by QUT (School of Nursing & Midwifery, QUT, Victoria Park Rd, Kelvin Grove, QLD 4059), Wesley Centre for Hyperbaric Medicine and Royal Hobart Hospital.

In Kind (staff): WCHM/RHH/QUT = \$824,000

In Kind (non staff): WCHM/RHH/QUT = \$351,012

In kind (equipment): WCHM/RHH = \$100,000

This study aims to conduct a double blinded, randomised, placebo-controlled trial to determine the effectiveness of hyperbaric oxygen therapy for patients with non-healing venous leg ulcers on progress in wound healing, pain, quality of life and cost effectiveness of care. Prior to commencement of the study a randomisation allocation sequence will be generated with a computerised randomisation program. Study participants will be block randomised according to ulcer size (over 10cm² or ≤10cm², based on research by Margolis et al.¹⁵).

Eligible trial participants :

Adult males and females with non-healing venous leg ulcers.

Inclusion criteria:

1. Leg ulcers of primarily venous aetiology
2. Ankle-brachial pressure index ≥0.8 and <1.3
3. Transcutaneous oxygen measurements indicative of a hypoxic wound that is responsive to an oxygen challenge (≤40mmHg on room air at 1ATA, with a response >100mmHg on 100% oxygen at 1ATA)
4. Ulcers that have not responded to standard treatment (high level compression therapy) i.e. with a ≥50% reduction in ulcer area after 4 weeks of compression dressings
5. Agree to comply with all study procedures

Exclusion criteria:

1. Leg ulcers of non-venous aetiology
2. Pregnancy
3. Reactive airways disease (COPD with CO₂ retention), radiographic evidence of pulmonary blebs/bullae
4. Untreated pneumothorax or history of spontaneous pneumothorax
5. Cardiovascular instability of known LVEF<35%

6. History of seizures
7. Delirium/dementia/inability to follow simple commands
8. Concurrent administration of disulfiram, doxorubicin or cisplatin
9. Prior chest surgery, middle ear surgery, optic neuritis, claustrophobia, or congenital spherocytosis.

Methods intended to minimise bias in the results of the trial,

Computer randomised by pre-prepared, sequentially numbered opaque envelopes.

Blinded (masking used): The people receiving the treatment/s via administration of active or placebo (sham) HBO treatments, The people assessing the outcomes, The people analysing the results/data (assignment: Parallel)

Patients, researchers, research assistants, and nurses providing treatment/data collection/outcome assessment will all be blinded to treatment/control arm allocation. Only the hyperbaric technician and in-chamber nurse attendant will be aware of the treatment allocations.

The placebo (sham) treatment protocol, has been independently validated by previous research.

Study Therapy:

Active - Oxygen at 2.4 atmospheres absolute for 110 minutes in the Hyperbaric Chamber.

Placebo (sham) - Exact time replica of the treatment protocol using air pressurised to 1.2 ATA then decreased to 1.05 ATA. This is repeated in a cyclical routine through the “compression/decompression” phases of the treatment protocol. The patient is maintained at 1.2 ATA through the 85 minute “treatment” phase.

Interventions compared:

Following a four week pre-HBOT assessment period (during which the patients receive optimal, standardized wound care and high level compression dressings), patients who don't have a >50% wound area reduction will be randomized into the RCT.

The study arm will receive 30 HBO treatments (2.4ATA, 100% oxygen, for 110min. each) over 6 weeks, followed by a further 6 weeks of standard wound care (or until the wound heals).

The control arm will receive 30 ‘sham’ HBO treatments (initial pressurization to 1.2ATA on air, followed by reduction to 1.0ATA on air) over 6 weeks, followed by a further 6 weeks of standard wound care (or until the wound heals).

It is planned to complete a total of 58 study participants (29 in each of the active and placebo group) in the randomised HBOT study. To date the study has recruited 46 patients to the trial with 12 meeting criteria and subsequently randomised to the HBOT/Sham intervention (ie 21% of required patients to date). Another 3 are about to be randomised.

Start date (first patient recruited) 30/08/2011

Anticipated finish date 30/08/2014 (Funding just achieved 2012)

Study Duration: Total of 16 weeks including the four weeks prior to and six weeks following the HBOT intervention of six weeks duration.

Objectives of the Study: To determine the effectiveness of hyperbaric oxygen therapy for study participants with venous leg ulcers that have failed to heal using standard treatment, on wound healing, pain, quality of life and cost effectiveness of care.

Outcomes: (see table below)

Primary outcome: incidence of complete wound closure at the completion of the study (12 weeks after starting HBOT)

Secondary outcomes: (a) time to wound healing, (b) ulcer area percentage reduction, (c) difference in PUSH scores, (d) cost effectiveness, (e) Quality of Life data (SF-12, MOSPM, GDS) will be measured at the beginning and end of the 16-week study.

Primary outcome 1:	Number of healed ulcers/group. Ulcer area will be calculated using wound tracings, digital photography and digital planimetry to determine area reduction, percent reduction and total healing rates. A healed ulcer is defined as full epithelialisation maintained for at least two weeks.
Timepoint:	Assessed every week up to 12 weeks from randomisation.
Primary outcome 2:	Time to ulcer healing
Timepoint:	Assessed every week up to 12 weeks from randomisation.
Primary outcome 3:	ulcer area percentage reduction in each group
Timepoint:	Assessed every week up to 12 weeks from randomisation.
Secondary outcome 1:	PUSH scores of each group (Stotts et al. 2001. J Gerontol Biol Sci 56:M795)

Timepoint:	Assessed every week up to 12 weeks from randomisation.
Secondary outcome 2:	Quality of life of each group, measured with: 1. SF-12 2. Medical Outcomes Study Pain Measures 3. Geriatric Depression Scale
Timepoint:	Upon enrolment in the study and at 12 weeks from randomisation.
Secondary outcome 3:	Cost effectiveness of each group will be evaluated by a health economist, utilising measures of the number and costs of health services provided, investigations, dressings and bandages used while unhealed, occasions of care provision and staff time, loss of functional ability and QALYs.
Timepoint:	At the completion of the study, 12 weeks after the initiation of the HBOT treatments.
Secondary outcome 4:	incidence of treatment emergent adverse effects for each group (e.g., ear barotrauma, oxygen toxicity effects such as seizures, myopic visual effects). These side effects are all temporary changes. A nurse is present with patients through all hyperbaric treatments and will check with the patient re whether they have any ear pain or other symptoms and treat and record any adverse effects. Patients will also be asked if they have had any of these symptoms at each study visit.
Timepoint:	at every HBOT or sham HBOT treatment.
Key inclusion criteria:	Persons presenting with a venous leg ulcer that have an Ankle branchial pressure index between 0.8 and 1.2, a TCOM reading that indicates a hypoxic wound responsive to an oxygen challenge (≤ 40 mmHg on room air at 1ATA, with a response > 100 mmHg on 100% oxygen at 1ATA), who are not at risk for hyperbaric-related complications and whose ulcer has not responded to standard treatment (i.e., $< 50\%$ reduction in ulcer area following 4 weeks of wound care and compression therapy > 35 mm Hg with layered compression bandaging).
Minimum Age:	18Years
Maximum Age:	No limit

Gender:	Both males and females
Healthy volunteers?	No
Key exclusion criteria:	<ol style="list-style-type: none"> 1. Persons with cognitive impairment. 2. Persons with an Ankle Branchial Pressure Index <0.8 or >1.2. 3. Persons with leg ulcers of non-venous aetiology. 4. Persons considered to be at specific risk for hyperbaric-related complications, as specified below: <ul style="list-style-type: none"> -pregnancy -concurrent administration of disulfuram, or antineoplastic agents doxorubicin and cisplatinium. -reactive airway disease (COPD with CO2 retention), radiographic evidence of pulmonary blebs/bullae -untreated pneumothorax or history of spontaneous pneumothorax -previous documented ejection fraction less than 35% or cardiovascular instability -history of seizures - except childhood febrile seizures -unable to follow simple commands, not orientated to person, place, time. -prior chest surgery, middle ear surgery, optic neuritis, fever, congenital , spherocytosis, claustrophobia.

Sample Size

Previous studies in this area have demonstrated that, of the study participants with venous leg ulcers who do not achieve at least 50% reduction in ulcer area in four weeks (i.e., the sample planned for this study), 25% are healed by 12 weeks. Therefore, assuming the control group will have approximately 30% healed, and aiming for 50% of the intervention group to be healed (to obtain a significant clinical difference), sample size calculations result in the following:

Following the four-week pre-HBOT standard best practice treatment for their ulcer, a total of 58 completing study participants (29 per group) eligible for randomisation will be required - 29 study participants per group are needed to detect a 20% difference between groups in the total numbers

of study participants healed (e.g., 30% healed in the control group vs. 50% in intervention group) after 12 weeks of intervention.

Allowing for 10% attrition over the 16 weeks of the study, at least 64 study participants would be required, as determined by power analysis and based on a significance level of 0.05 and power 90%.

Based on previous studies with community living study participants with venous leg ulcers, approximately 30% will achieve at least 50% reduction in ulcer area in the first four weeks, therefore, to obtain a sample of 64 study participants eligible for randomisation, at least 84 study participants will need to be recruited and enrolled into the four-week pre-HBOT treatment assessment period of the study.

Analysis Plan

All participants enrolled in the study will be included in summaries of subject disposition, but study participants who discontinued prior to randomisation into the HBOT study will be excluded from all other aspects of the analyses.

This study will be analysed by Intention –to-treat principles, in addition to a per-protocol (PP) efficacy sub-set analysis.

To be eligible for inclusion in the ITT population, study participants will have been randomised into the HBOT study, and have at least one post-randomisation evaluation for the variable concerned. If a study participant was inadvertently administered an incorrect treatment the analyses will be performed assuming the study participant was treated as randomised. Study participants withdrawn from the study prior to Week 6 will be censored at the time of withdrawal in the Cox proportional hazards regression and included in the ITT analyses. Study participants with missing data regarding healing response at the end of the study (week 16) will be classified as lost to follow-up and excluded from the logistic regression analysis on proportions/group healed, however will be censored at the time of dropout and included in the ITT survival analysis.

The PP population will be a sub-set of the ITT population. This subset will restrict eligibility to those study participants who complete the 6 Week HBOT Treatment Period of the study (attending at least 4 days/week) or who reach complete healing prior to Week 6. Their efficacy measures will have been taken. at appropriate times and under appropriate conditions and they will not have violated or deviated from the Protocol in any manner that may impact the efficacy assessments.

Criteria for determining major Protocol violations will be reviewed by QUT upon completion of the clinical phase of the study and all study participants to be excluded from the statistical analysis will be identified. When all decisions regarding assignment have been made a final list of study participants to be excluded from each population will be prepared. QUT will approve this list before the study blind is broken.

The main population upon which effectiveness conclusions will be based will be the ITT population. The PP population will be used to support the conclusions reached. Analyses will be performed on only the ITT population if the PP subset contains more than 95% of the ITT population.

Data cleaning, consistency checking and management of missing data

Frequency distributions and histograms of all variables will be run to check for invalid, missing and inconsistent values. The pattern of missing data will be checked by testing differences between cases with missing data and cases with no missing data. Missing Scale date will be treated as per the authors' instructions. Outliers will be checked against the raw data for accuracy and extreme outliers will be retained with their values altered to the mean or median to reduce the deviance and thus any impact on causing errors. 19

Data analysis

The primary outcome, proportions of participants healed in each group, will be analysed using a multivariable logistic regression. Descriptive analyses will be undertaken for all variables. Bivariate relationships will be tested with Chi-squared tests, independent *t*-tests or Mann-Whitney *U* tests to examine relationships between whether healed or not and demographic, medical, venous, ulcer, pain, depression and quality of life variables. The data will be checked for fit with the assumptions of logistic regression (i.e. adequacy of expected frequencies, independence in responses, multicollinearity, linearity in the logit). Outliers from the model with standardised residuals higher than 3 will be removed from the analysis. All variables significantly associated with healing ($p < 0.05$ level) or previously identified in the literature as influencing healing will be entered into a multivariable logistic regression model to determine their independent influences on healing.

Secondary Outcomes: Time to healing will be analysed using a Cox Proportional Hazards multivariable regression model.

Quality of Life and Pain measures outcomes will be analysed using repeated measures ANCOVA. Percentage ulcer area reduction will be analysed using ANCOVA.

Cost Effectiveness analysis will be undertaken using measures of costs of service provision, wound dressings, bandages, and time to healing. Quality of life data will also be used to estimate preference based valuations of health outcome.