# Work in progress

## The outcome of chronic wounds following hyperbaric oxygen therapy: a prospective cohort study – the first year interim report

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**Key words**
Chronic wounds, hyperbaric oxygen therapy, research

**Abstract**

(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.)
**Introduction:** The treatment of chronic wounds is a major health cost. This study is an ongoing prospective cohort looking at the effects of hyperbaric oxygen therapy (HBOT) on the healing of chronic wounds.
**Methods:** Data are being collected from patients presenting to hyperbaric facilities in Australia with chronic (>3 months' duration) non-irradiated wounds, including details of aetiology, wound characteristics and possible predictors of wound healing. Participants are being enrolled whether or not a decision was made to treat with HBOT. Assessments are performed at the end of the course of HBOT and at one, six and 12 months post hyperbaric treatment. The aim is to quantify the proportion healed and to identify any significant predictors for wound healing.
**Results:** There are 110 participants included in this analysis with 88 receiving HBOT. Excluding the miscellaneous aetiologies, at the end of treatment 52.3% of patients had a 'good' outcome to the wound, increasing to 64.1%, 91.7% and 78.2% at one, six and 12 months respectively. Logistic regression for participants with diabetic wounds suggests that wound area, chronicity and transcutaneous oxygen readings on room air combine to produce a statistically significant model for prediction of wound healing at one month after treatment.
**Conclusions:** This ongoing cohort study suggests that HBOT is highly associated with the healing of chronic wounds in the patients in this study. The wound area at presentation, the duration of the wound and the transcutaneous oxygen pressure on air may predict the likelihood of a chronic wound in diabetic patients healing by one month after treatment.

### Introduction

Chronic wounds are defined as an interruption in the continuity of the skin where conventional treatment has not achieved healing within a reasonable time (e.g., 3 months).[1] Such wounds are an increasing burden on healthcare systems throughout the world. Studies have shown a prevalence in hospital patients of up to 24%, and 2% of the general population have some form of chronic wound at any one time.[2–5] This creates a significant financial burden on funding agencies with costs exceeding several billion dollars per year.[6–8] There are compelling reasons to deliver treatment modalities that are cost effective to individuals with such wounds.

Treatment regimens for chronic wounds are multi-modal but have been traditionally of two types: specific treatments designed to reduce the effect of the underlying disease (such as tight glycaemic control in diabetics and compression bandages in venous insufficiency), and wound environment optimisation dressings (e.g., hydrocolloid gels and antibacterial impregnated dressings).

The rationale for adjunctive hyperbaric oxygen therapy (HBOT) in chronic wound care is the premise that the underlying problem in many of these wounds is hypoxia. While acute wounds require low oxygen tensions, low pH and a high lactate load to initiate angiogenesis and wound healing,[9,10] later phases of healing are critically dependent on oxygen, e.g., fibroblastic collagen deposition and macrophage bacteriocidal activity.[11–13] It has been suggested that the stimulus for healing is a rapid drop in the partial pressure of oxygen from surrounding healthy tissue to the wound. In chronic wounds there is a much more gradual drop across the wound margin and this may inhibit healing significantly.[14]

The Medicare Services Advisory Committee (MSAC) was established in 1997 to advise the Australian Minister for Health and Ageing on the safety and cost effectiveness of new medical technologies and procedures, and to make recommendations for funding under the Medicare Benefits Scheme.[15] One such review was initiated into the provision of HBOT, and in 2001 MSAC recommended that a properly conducted prospective trial should be undertaken on the treatment of chronic non-irradiated wounds with HBOT. This report presents the first results of a prospective cohort of patients enrolled since June 2004.

## Methods

All hyperbaric facilities in Australia and New Zealand were invited to participate in the study. There are currently 13 such chambers treating patients for chronic wounds. Three facilities (Prince of Wales Hospital, Sydney (POW), The Wesley Hospital, Brisbane (WES) and Royal Hobart Hospital, Hobart (HOB)) have been able to start in the first year and three other facilities are currently awaiting ethics approval or the conditions of their approval have not permitted submission of data in the first year. No enrolments were undertaken prior to obtaining approval from the relevant local ethics committee. Data were collected on each patient by each facility and an identifying number was included in the data collection sheet that allowed each centre to follow individual patients' progress through the four reporting stages. At the collection centre (POW) each individual patient was given a code number to identify the enrolling centre they were from and order of enrolment. Analysis was performed on the POW code numbered datasheets entered into a computer database.

### PATIENT SELECTION

All patients referred to a hyperbaric facility for assessment of one or more chronic wounds (present for more than three months) are eligible for inclusion, regardless of prior therapy. Patients considered unsuitable for HBOT due to the presence of a contra-indication, inadequate prior therapy or anticipated lack of response are therefore also eligible for enrolment. Acute (including extensive debridement within three months) wounds and those due to irradiation tissue injury are excluded from the study. The study authors did not determine assessments or impose HBOT treatment schedules on the study centres as there is no definitive treatment schedule that has been shown to be better than any other. We also feel that this allows the study to reflect 'true practice' in the hyperbaric field, with the variety of equipment currently available in each centre also influencing clinical practice.

### DATA COLLECTION

A standardised datasheet was developed that recorded demographic data, possible contributing factors to poor wound healing, treatment up to the date of assessment, subsequent hyperbaric treatment (if performed) and outcome immediately following HBOT as well as at one month, six months, and twelve months after HBOT.

Data were collected on a Filemaker Pro™ database (Filemaker Inc, Santa Clara, California). Each patient was given a designated identification number for tracking through the four assessment times. Each facility is responsible for data collection on the subjects enrolled at that facility. Units are being encouraged to use all means at their disposal to locate missing subjects, including direct contact and through their local medical services and family members. Each unit was reminded at the appropriate times when a patient was due for re-assessment.

**Table 1**
**Clinical outcome scores for wounds**

| Clinical description | Category | Outcome class | Outcome |
|---|---|---|---|
| Deceased | 1 | No benefit | BAD |
| Nil benefit ± major amputation | 2 | | |
| Minimal benefit + minor amputation | 3 | Some benefit | |
| Improved + minor amputation | 4 | | |
| Substantially healed | 5 | Healed | GOOD |
| Healed | 6 | | |

### OUTCOMES

Outcomes are scored on a six-point scale originally developed by Dr Harry Oxer (Davis FM, personal communication, 2003) at Fremantle Hospital Hyperbaric Medicine Unit. However, for this interim assessment we categorised all outcomes as either 'good' or 'bad' as shown in Table 1. We have specifically placed amputations of any sort into the 'bad' outcome category because this seems an appropriately conservative approach to assessing the effectiveness of HBOT. While an amputation may indicate a good outcome (e.g., saved limb but lost toes) or poor outcome (e.g., superficial foot ulcer but lost toe) there may be no clear indication which is the case for any individual patient. In addition, any amputation will alter the location and dynamics of the wound – essentially converting a chronic wound into an acute surgical wound. We planned an annual analysis for reporting back to the contributing units.

### WOUND CATEGORIES

Wounds were allocated to one of four main aetiological categories for analysis – diabetic (DM), peripheral vascular disease (PVD), venous disease and miscellaneous (including vasculitic and auto-immune diseases). Because the miscellaneous group contains highly diverse aetiologies in very small numbers, no analysis of the fate of this group has been undertaken in this interim report. Similarly, this report does not compare the chance of a good outcome with and without HBOT because of the small numbers in the non-HBOT group.

### STATISTICS

No sample size calculations were performed for this study, as it is an ongoing opportunistic cohort study. We performed

a descriptive statistical analysis and a backward stepwise logistic regression analysis on each aetiological group for factors that may predict wound outcome. This was done in order to develop a predictive model for wound healing after HBOT. All calculations were performed using StatsDirect v2.4.5 (StatsDirect Ltd., StatsDirect statistical software. <http://www.statsdirect.com> England: 2002).

## Results

There were 110 patients enrolled in the study of whom 88 received hyperbaric oxygen treatment. Sixty-seven (61%) were males and 43 (39%) females. The group receiving hyperbaric oxygen had 54 (61%) males with an average age of 67.2 years. The group that did not receive hyperbaric oxygen had 13 (59%) males with an average age of 70.4 years. The breakdown by aetiology is shown in Table 2.

### HYPERBARIC TREATMENT

The average number of treatments for the patients receiving HBOT was 24.4 (range 1–70). The average number of treatments, for each aetiology, is given in Table 3, while the overall frequency distribution is shown in Figure 1.

**Table 2**
**Number of patients and mean ages (with range) of all patients enrolled in the study (whether they had HBOT or not) by aetiology**

| Aetiology | Number | Average age years (range) | % total wounds |
|---|---|---|---|
| DM | 46 | 66.4 (42–89) | 41.8% |
| PVD | 27 | 73.9 (37–91) | 24.5% |
| Venous | 18 | 69.2 (43–87) | 16.4% |
| Miscellaneous | 19 | 61.7 (11–83) | 17.3% |
| **Total** | **110** | **67.8 (11–91)** | **100%** |

(DM – diabetes mellitus; PVD – peripheral vascular disease; venous – venous insufficiency)

**Table 3**
**Number of patients and treatment averages of those patients who had HBOT by aetiology**

| Aetiology | Number of patients | Mean number of treatments (SD) |
|---|---|---|
| DM | 40 | 23.4 (10.2) |
| PVD | 20 | 24.7 (8.46) |
| Venous | 13 | 24.2 (9.49) |
| Miscellaneous | 15 | 27.0 (14.63) |
| **Total** | **88** | **24.4 (10.53)** |

(DM – diabetes mellitus; PVD – peripheral vascular disease; venous – venous insufficiency)

### OUTCOME DATA

Figure 2 shows the percentage of people in each aetiological group with a 'good' outcome (Scores 5 and 6, Table 1). Overall, immediately after the HBOT course, 52.3% of all aetiological groups combined had a 'good' outcome and this proportion increased to 64.1%, 91.7% and 78.2% at one, six and twelve months respectively. These data suggest that diabetic wounds improve most rapidly following HBOT, with venous wounds catching up at one month and arterial wounds at six months. At the time of the final draft of this interim report, we have follow-up data on 60% of those enrolled, and 43% at one year. Because these data sets are substantially incomplete, they will be reported in future annual analyses.

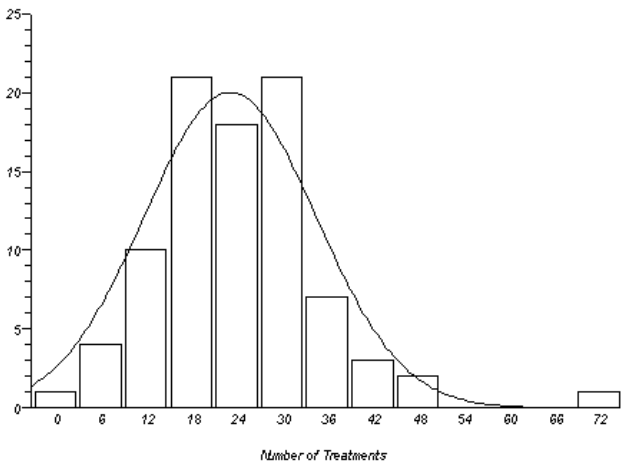
Because of the small numbers enrolled in the study, regression analysis for outcome was possible only for those patients with diabetes mellitus. We performed univariate analysis and a logistic regression for 'good' outcome at the end of HBOT and at one month after HBOT with the potential predictors being gender, duration of wound (months), wound area ($cm^2$) transcutaneous partial pressure of oxgyen ($P_{tc}O_2$) in air (mmHg) and $P_{tc}O_2$ on 100% oxygen at 1 ATA for 10 minutes (mmHg). Neither at the end of HBOT nor at one month follow up were there any significant predictive factors identified on univariate analysis. Stepwise logistic regression for healing at the end of the HBOT course did not produce a useful model. However, analysis at one month follow up suggested the following model was predictive of healing:

$$\text{Log (OR)} = 2.30 - (0.09*\text{TWA}) - (0.11*\text{DUR}) + (0.06*P_{tc}O_2)$$

where TWA = total wound area in $cm^2$, DUR = duration of wounds in months and $P_{tc}O_2$ = transcutaneous partial pressure of oxygen on air at 1 ATA in mmHg.

This model suggests that, at presentation, wound healing is negatively impacted by increased wound area, duration of

**Figure 1**
**Frequency distribution (with curve of best fit) of number of treatments for patients receiving HBOT**



wound and a lower $P_{tc}O_2$ in air. For example, using this model we would predict that for a wound 7 $cm^2$ in area and of 10 months' duration with a resting $PtcO_2$ (in air) of 30 mmHg, the odds of healing at one month after completion of a course of HBOT are nearly 11 to one (odds ratio 10.7).

**Discussion**

This study suggests that we can expect 50% of chronic wounds to heal by the end of a course of HBOT and up to 90% of wounds to be healed at six month follow up. These wounds have all persisted for at least three months at presentation despite comprehensive wound care, and we believe this represents a real and important clinical benefit. Although 50% may not seem a particularly large proportion, given the population of Australia (20,404,617)[16] and an assumed prevalence for chronic wounds of 1%, this represents over 100,000 people who could potentially have a good outcome from HBOT.

Hyperbaric facilities have been treating chronic wounds for several years but there has been very little high-quality clinical research evidence to demonstrate the effectiveness of HBOT. A recent Cochrane meta-analysis on the efficacy of HBOT for chronic wounds included four randomised controlled trials (RCTs).[1] Three of these studies enrolled diabetic foot ulcer patients and one enrolled patients with venous ulcers. There were no RCTs on the effects of HBOT on arterial ulcers. These RCTs suggest that there was a benefit in having HBOT for diabetic and venous ulcers but a larger, multi-centre study is required.

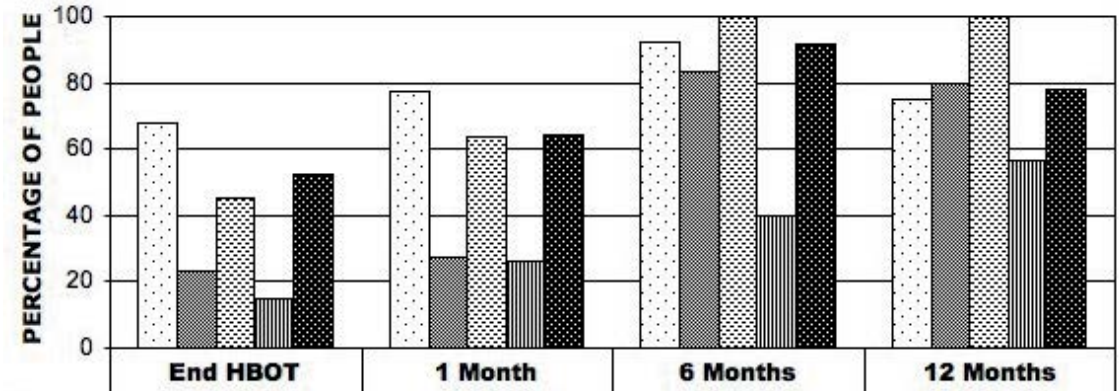
Because of the small number of patients enrolled in this study who did not receive HBOT (n = 22), we have not reported the fate of ulcers in that subgroup of patients in this analysis. While the reasons they were thought unsuitable for HBOT were not always clear, we hypothesise most of them had normoxic $P_{tc}O_2$ levels, failed to adequately respond to oxygen challenge with an increase in $P_{tc}O_2$ or declined to undergo therapy. We intend to more fully address this group in our next report.

There are differences in response to HBOT between aetiologies. Diabetic wounds have a faster resolution (higher percentage of those with a good outcome at the end of treatment) and appear to have a higher chance of a good outcome for the first few months after treatment. The estimated difference narrows rapidly and at six months there is very little between the three main aetiologies.

Logistic regression suggests that even with this small data set, we are able to show that features such as total wound area, duration of wound and $P_{tc}O_2$ at the wound site breathing air at 1 ATA are significant predictors of the proportion of wounds that will heal. We hope that as the data set grows, the regression model will become increasingly predictive of those wounds that can be expected to heal. This would have useful clinical applications for the selection of candidates for HBOT.

There are several limitations to the interpretation and applicability of this study. First among them is the loss of data as the study progresses. This is largely due to inability to contact some patients for follow up, despite considerable efforts to do so. Currently 56.6% of patients' data are lost at the 12-month assessment time reflecting difficulties in following up patients out to this time period. We have attempted to address this with better patient tracking and by

**Figure 2**
**Number of people with 'good' outcome after HBOT as a percentage of total people receiving HBOT**




| | End HBOT | 1 Month | 6 Months | 12 Months |
|---|---|---|---|---|
| TES | 67.6 | 77.4 | 92 | 75 |
| | 23.5 | 27.3 | 83.3 | 80 |
| IS | 45.5 | 63.6 | 100 | 100 |
| IISSING | 15.1 | 26.4 | 40 | 56.6 |
| OUNDS | 52.3 | 64.1 | 91.7 | 78.2 |

ASSESSMENT TIME

co-ordinating the follow up of patients with active reminders to the collection centres involved. Some apparent loss of data is in fact due to significant numbers of participants who have not yet reached the final assessment time.

Another significant limitation for this cohort study is the relatively small number of participants who had chronic wounds but did not receive HBOT. Financial considerations have made it impractical to improve the methodology of this study by the active recruitment of a comparison cohort of participants for whom hyperbaric referral has not been considered. Such a study is beyond our means at this time but remains highly desirable.

In conclusion, we have reported the first 110 patients of an ongoing prospective study. Our results suggest that a clinically important proportion of patients can expect a good outcome by one month after the completion of hyperbaric therapy. We continue to collect data prospectively and hope to generate a useful predictive model by which to identify those patients in whom HBOT is appropriate. We believe that this study is important in helping to better define the role of hyperbaric oxygen in these patients.

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