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

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ABSTRACT:

We report data from the sixth year of the ANZHMG prospective cohort study of wound outcomes after hyperbaric oxygen therapy (HBOT). All patients attending a hyperbaric facility with a wound of greater than three months duration (other than associated with radiotherapy) were eligible for inclusion. Assessment points of the study are; at the end of HBOT, 1 month post HBOT, 6 months post HBOT and 12 months post HBOT. Currently, 441 patients have been enrolled with 355 of them receiving 5 or more hyperbaric oxygen therapy treatments. The people who received HBOT had wounds for an average of 19.9 months and a mean area of 18.2cm^2, while those who did not receive HBOT were of 14.3 months duration and 26.9 cm^2 in size. At each assessment time, all wounds were classified as either 'Good Outcome' or 'Poor Outcome' based on a pre-determined wound score. At the 6 year mark, across all aetiologies, the percentages of patients with a 'Good Outcome' at each assessment period was 43.9%, 54.2%, 68% and 80.4% respectively.

Our study suggests 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.

INTRODUCTION:

This is a report of the results six years into the ongoing Australia and New Zealand Hyperbaric Medicine Group (ANZHMG) Wound Care Study, which was initiated in June 2004. The study methodology has been presented in detail previously.[1]

A chronic wound may be defined as any interruption in the continuity of the body's surface that requires a prolonged time to heal, does not heal, or recurs.[2] These wounds remain a common and expensive health problem. The true incidence and impact are difficult to assess because much care is delivered at home and wound care products are purchased from a variety of sources. The prevalence of wounds is high, and in the UK has been estimated at up to 12% of the aged population and the annual cost to be in excess of £1billion annually.[3,4]

Not surprisingly, there are a very large range of wound care techniques and specialised dressings available to assist with management of these wounds. Strategies include treatment of the underlying pathology (e.g. blood glucose control in diabetes), systemic treatment aimed at improving the local wound environment (e.g. nutrition supplements) and local treatment aimed at improving the wound environment (e.g. dressings). As noted in a Cochrane review of the subject, 'in practice, wound management is often a sequential and fruitless search for a successful combined approach'.[5] In this environment, it is of great importance to accurately assess the success or failure of each treatment strategy.

It is the aim of the current study to examine the fate of chronic wounds referred to hyperbaric facilities in Australia and New Zealand and if possible, develop a predictive model for successful outcome that may assist with future patient selection.

METHODS:

A full description of the methods and statistical approach has been previously published.[1] All hyperbaric facilities in Australia and New Zealand have been invited to participate in the study and currently of the fourteen facilities, ten have returned data collection forms. All locations obtained local ethics committee approval prior to the commencement of collecting data (details available on application to the author).

PATIENT SELECTION:

All patients presenting to a participating hyperbaric unit for assessment of a chronic wound (defined as a wound of greater than three months duration) were eligible to be included in the study regardless of aetiology (with the exception of radiation injury) or prior therapy. Following informed consent, the patients were assessed according to the procedure in place at

each facility and data was collected on a standard data collection template developed for this study, which was available in both a paper and electronic format. If multiple wounds were present, a reference wound was chosen for inclusion in the study. All patients presenting for assessment were eligible for inclusion, regardless of any decisions regarding therapy. In particular, there was no requirement for the individual to be suitable for HBOT. Wounds were classified into one of four aetiologic categories for subgroup analysis: diabetic (DM); peripheral vascular disease (PVD); venous disease and miscellaneous.

Specific exclusion criteria included acute wounds (ie less than three months duration), wounds that had surgical intervention within the last three months and wounds associated with exposure to radiation.

Any therapy instituted for patients enrolled in the study was at the discretion of the medical staff responsible in each unit, and no attempt was made to standardise the approach to wound care in general or the HBOT schedule in particular.

Each patient was de-identified before data was transmitted to Prince of Wales Hospital for collation. A unique code was generated to allow backtracking and identification at the enrolling site in order to allow future analysis and comparison of results for different units. All data was transferred to a Filemaker Pro Advanced v11.0 database (Filemaker Inc, Santa Clara, California, 2010).

OUTCOMES:

The primary outcome was the degree of healing assessed by a six-point scale originally developed at Fremantle Hospital (Table 1). For this interim assessment, we have dichotomised the outcome into ‘Good’ (completely or substantially healed) or ‘Bad’ (any other outcome score).

<<INSERT TABLE 1 AROUND HERE>>

This approach is a conservative one that is likely to classify some patients who do functionally well as a poor outcome (for example, any patient requiring a minor amputation but who do eventually heal)

STATISTICAL ANALYSIS:

No sample size calculations were performed for this study, as it is an ongoing opportunistic cohort study. All calculations were performed with StatsDirect v2.7.8 (StatsDirect Ltd, StatsDirect statistical software. <http://www.statsdirect.com> England, 2010). We compared normally distributed continuous data means using Student's t-test and Chi^2 for the comparison of proportions between groups.

RESULTS:

There are currently 441 patients enrolled in the study of whom 355 have received five or more hyperbaric treatments. Other characteristics of the patient populations are listed in Table 2. The reference wounds had been present significantly longer (mean 19.9 months versus 14.3 months, $P = 0.03$) and tended to be smaller in area (mean 18.2 cm^2 versus 26.9 cm^2, $P = 0.08$) in those selected for HBOT than those not thought suitable for HBOT.

Of those who received HBOT, the average number of treatments for all groups was 28.2 with a range of 6-70. The 'Miscellaneous' group was the most variable in this regard.

<< INSERT FIGURE 1 AROUND HERE>>

There are three main treatment peaks around 20, 30 and 40 treatments, indicating the standard treatment regimens in use at most hyperbaric facilities (see Figure 1).

<<INSERT TABLE 2 AROUND HERE>>

The overall outcomes at each time point for the patients who received HBOT are summarised in Table 3. The overall proportion of patients with a good outcome at the one year assessment was 80.4%. Wounds in patients with diabetes mellitus remain the largest aetiological group (36.1%), while those associated with peripheral vascular disease accounted for 25.1%, the miscellaneous group 22.8% and those associated with venous disease 16.1% of the total.

<<INSERT TABLE 3 AROUND HERE>>

All aetiologic groups showed an increasing proportion of patients with a good outcome over the 12 months following treatment with HBOT. Patients with either diabetes or venous disease as their primary aetiology, had healing rates in excess of 85% at twelve months (see Table 4.)

<<INSERT TABLE 4 AROUND HERE>>

DISCUSSION:

This prospective cohort study suggests the majority of patients given HBOT for a chronic wound in Australia and New Zealand will achieve a good outcome at one year, regardless of aetiology. This is consistent with the findings of randomised controlled trials on the subject.[6-11] The inclusion criteria are broad and we have deliberately adopted this position in order that our results might reflect actual clinical practice in the real world. Given the strong evidence base for the treatment of radiation tissue injury, we have specifically excluded such wounds to avoid positive confounding of the overall result by a strongly positive result in this group. Similarly, we have excluded patients with acute wounds that might be expected to heal once adequate perfusion has been established and tissue disruption/infection has been appropriately treated.

The group of chronic wounds included are indolent (averaging almost 20 months in duration for the HBOT group and over 14 months for the non-HBOT group) and almost universally have received competent and intensive therapy including vascular assessment, diabetic control, antisepsis, appropriate debridement and wound dressing prior to referral. Indeed, perhaps because of limited availability, the inconvenience of time-consuming therapy sessions and perceived high short-term costs, many patients have been referred to hyperbaric centres as a treatment modality of 'last resort'. We would expect the predicted chance of achieving a good outcome in these patients to be quite low. In this setting, a 40% chance of a good outcome at the end of HBOT, rising to over 80% at one year, would seem to be very positive.

This ongoing study continues to predict that nearly half of the patients presenting to a hyperbaric facility with a chronic wound can expect to attain a good outcome immediately at the end of a course of hyperbaric treatment. This response rate is clinically significant given the length of time for which these wounds have been present before referral. This observation confirms a number of previous reports and a Cochrane review[8] where HBOT has been associated with good outcomes in chronic wounds.

Outcomes continue to improve for at least 12 months following treatment, and this is consistent with the angioneogenic effects of hyperbaric oxygen seen in a radiotherapy model by Marx et al[12,13] and the positive modifications to the wound milieu demonstrated by Thom, Hunt, Niininkoski and many others.[14-16] Based on our results, at one year after presentation we expect over 80% of all people who present to a hyperbaric facility for wound care assessment and receive more than five HBOT treatments to have a substantially or completely healed wound regardless of aetiology. In the case of people with diabetic ulcers and patients with venous ulcer disease we would expect the rate to exceed 85%.

Not surprisingly, the rate at which wounds heal varies with aetiology. Venous ulcers resolve faster than diabetic wounds for example, and the disparate group of miscellaneous wounds and primary peripheral vascular disease heal most slowly of all on average.

Analysis of the patients that did not have HBOT remains hampered by small numbers and the fact that the assessing centres did not always record why the patients were not offered treatment with HBOT. This shortcoming is being actively addressed for future reports. There are potentially two main reasons that HBOT might not be offered to a particular individual, and the implications for each would lead to opposing conclusions. First, it may be that oxygen supply was not the limiting factor for wound healing (ie. transcutaneous oxygen measurement was normal) and these patients may have a good outcome through the optimisation of other wound therapies. On the other hand, the clinical situation might be so grave as to make HBOT inappropriate – for example when immediate major amputation is indicated. The first subgroup might be expected to do better than the HBOT group, whilst the second would be likely to have worse outcomes. A direct comparison of outcome between groups in this study would not be a valid test of the true impact of HBOT on those patients for whom it is routinely applied.

Table 3 indicates a falling follow-up rate over time. While this is partly due to true loss to follow-up, much is due to patients not yet reaching the time for follow-up and this artefact will be addressed at the conclusion of the study. Some true loss to long-term follow-up is inevitable as many of these patients must travel great distances to reach the State hyperbaric facility. We have tried to reduce this source of data loss by both thorough tracking of patient codes and enrolling local doctors to do the assessment for us under direction. Whilst our

confidence in the results for those receiving HBOT increases as we increase the numbers of participants, the same does not necessarily apply to the fate of the group who did not receive HBOT. Perhaps unsurprisingly, a relatively small proportion of patients referred to a hyperbaric facility are unsuitable for HBOT. Whether this is a consequence of careful referral from knowledgeable primary medical teams, or because of a low threshold for therapy is not clear. We continue to collect data on this group and hope to report more meaningfully in the future.

In conclusion, we have reported the first 441 patients at the six-year mark of our ongoing prospective cohort study. Nearly 50% of patients presenting with chronic wounds have a 'Good Outcome' immediately after HBOT regardless of aetiology. At 12 months following HBOT this increases to over 80%, despite the average duration and size of the wounds being 20 months and 18cm^2 respectively. Indeed, it is possible the results following HBOT would be even better if wounds had been referred at an earlier stage. We believe this study strongly suggests a benefit of HBOT for chronic wounds and we continue enrolment in an attempt to identify a useful predictive model to assist with patient selection.

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CLINICAL DESCRIPTION	CATEGORY NUMBER	OUTCOME CLASS	OUTCOME
Deceased	1	No benefit	BAD OUTCOME
Nil benefit ± major amputation	2		
Minimal benefit ± minor amputation	3	Some benefit	
Improved ± minor amputation	4		
Substantially healed	5	Healed	GOOD OUTCOME
Completely healed	6		

Table 1: Clinical outcome scores. Only patients with 'Good Outcome' were considered successful

	RECEIVED HBOT	**NO HBOT**
PATIENTS	355	86
M:F	196:159	46:40
AVERAGE AGE (Range)	69.29y (18-96y)	69.17y (11-94y)
AVERAGE WOUND SIZE (cm^2)	18.20 (s.d. 31.06)	26.90 (s.d. 35.40)
WOUND DURATION (months)	19.94 (s.d. 35.05)	14.32 (s.d. 23.28)

Table 2: Patient demographics

"Received HBOT": Has had at least 5 hyperbaric treatments

"No HBOT": Has had less than 5 hyperbaric treatments

s.d. = standard deviation

M:F = Male to Female ratio

	END HBOT		1M POST HBOT		6M POST HBOT		12M POST HBOT	
	HBOT (N=346)	No HBOT (N=30)	HBOT (N=306)	No HBOT (N=55)	HBOT (N=241)	No HBOT (N=43)	HBOT (N=163)	No HBOT (N=29)
GOOD OUTCOME (Scores 5 & 6)	152	11	166	24	164	25	131	17
POOR OUTCOME (Scores 1-4)	194	19	140	31	77	18	32	12
MISSING DATA*	9	56	49	31	114	43	192	57
% GOOD OUTCOME**	43.9%	36.7%	54.2%	43.6%	68.0%	58.1%	80.4%	58.6%

Table 3: Numbers of patients healed by each time period with percentage and missing data points. *Missing data includes those lost to follow up and patients not yet reaching assessment point. **Excludes missing data

AETIOLOGY	NUMBER	RECEIVED HBOT	PERCENTAGE WITH "GOOD OUTCOME"			
	(N)	Mean number of treatments and (s.d.)	END HBOT	1M POST HBOT	6M POST HBOT	12M POST HBOT
DM	128	26.0 (10.0)	43.9	53.7	74.7	85.7
PVD	89	29.1 (10.1)	39.8	55.6	66.0	71.4
VENOUS	57	29.1 (11.7)	52.7	57.7	68.3	85.2
MISC.	81	29.6 (10.2)	40.8	52.3	62.7	78.0
TOTAL	**355**	**28.2 (10.5)**	**43.9**	**54.2**	**68.0**	**80.4**

Table 4: Break down of improvements by aetiology and the mean and standard deviation of number of treatments required.

(N)= absolute number, s.d. = standard deviation

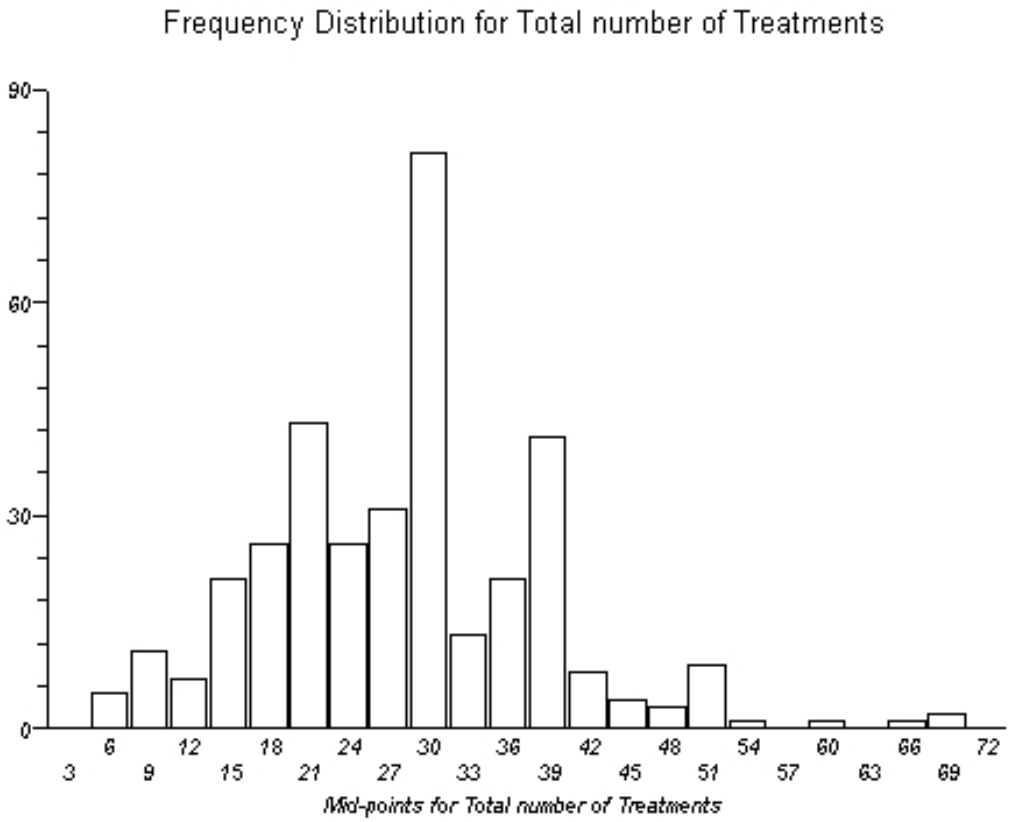

Figure 1: Grouped frequency distribution of treatment numbers.

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