Hyperbaric Oxygen Reduced Size of Chronic Leg Ulcers: A Randomized Double-Blind Study

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To evaluate the effect of hyperbaric oxygen therapy on chronic wound healing, 16 otherwise healthy patients who had nondiabetic, chronic leg ulcers with no large vessel disease were included in a double-blind study. Patients were grouped according to age and then randomly assigned to two groups breathing either air or oxygen at 2.5 atmospheres of absolute pressure for 90 minutes 5 days per week for a total of 30 treatments. The wound area was copied onto transparent film covering the wound and then measured using only one matching wound from each patient. The mean decrease of the wound areas at weeks 2, 4, and 6 in the oxygen group were 6 percent (SD ± 14), 22 percent (SD ± 13), and 35.7 percent (SD ± 17), respectively, and in the air group, 2.8 percent (SD ± 11), 3.7 percent (SD ± 11), and 2.7 percent (SD ± 11), respectively, 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 using the Mann-Whitney U test. These data indicate that hyperbaric oxygen therapy may be used as a valuable adjunct to conventional therapies when nondiabetic wounds do not heal. (*Plast. Reconstr. Surg.* 93: 829, 1994.)

The aim of this study was to evaluate the effect of hyperbaric oxygen therapy on chronic wound healing. Nondiabetic leg ulcers with no signs of large vessel disease were chosen in order to exclude arterial perfusion disturbances as a factor in the pathogenesis of the chronic wound.

Background

In 1965, Slack and coworkers[1] demonstrated the effect of hyperbaric oxygen on the healing of chronic venous ulcers. They treated 17 patients at 2.5 atmospheres of absolute pressure (ATA) once a day in a one-person chamber until maximal benefit was achieved. In their series, 65 percent of the ulcers either healed completely or showed marked improvement. In 1970, Bass[2] published similar results using 19 patients. They were treated at 2.0 ATA for 5 days a week. The number of treatments per patient ranged from 16 to 200, with a mean of 60.7. The wounds of 17 patients (89 percent) healed completely. In 1967, Perrins[3] showed a significantly increased surviving area of split thickness skin grafts as an effect of hyperbaric oxygen therapy in a randomized open study.

Kivisaari and Niinikoski[4] concluded, in controlled studies on rats, that hyperbaric oxygen had no effect on the healing rate of full thickness wounds in which the circulation was intact. In devascularized wounds, however, the retarded healing rate approached that of normal healing when hyperbaric oxygen was used.

In 1990, Oriani et al.[5] found a significant decline in amputation rates for diabetic gangrene in the hyperbaric oxygen group (5 percent versus 33 percent) in an open study.

In a search of the literature, no controlled study has been found regarding the effects of hyperbaric oxygen on chronic wound healing, although Marx[6] showed an ingrowth of new capillaries in radiation damaged tissue during 4 to 6 weeks of hyperbaric oxygen treatment, which made these tissues capable of healing a newly opened surgical wound.

The rationale for the use of hyperbaric oxygen is improved healing by elevating tissue oxygen tension intermittently within the wound, resulting in increased collagen forma-

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tion, enhanced fibroblast replication, and improved leukocyte function.[7,8]

Materials and Methods

Patients

Sixteen patients with leg ulcers of more than 1 year's duration were included (nine males and seven females, aged 42 to 75 years, median age 67 years). All patients gave informed consent to take part in the double-blind study as outpatients. The study was accepted by the Ethical Committee of the University of Lund.

Entrance Criteria

The distal blood pressure at the ankle and the first digit had to be within normal ranges ($\geq$100 percent and $\geq$70 percent, respectively, of the upper arm blood pressure in mmHg) as measured by ultrasound Doppler and blood pressure tourniquet. All patients continued their treatment (elastic stockings, etc.) prescribed by their personal physician and nurse throughout the study.

Exclusion Criteria

Patients with a smoking habit or concomitant chronic conditions (e.g., diabetes mellitus, collagen disease) were not accepted. The ulcers studied were not to have shown any tendency to heal (by visual inspection) during the 2 months before the study.

Methods

A multiplace pressure chamber was used with a double mask breathing system (Scott Masks). Either air or oxygen was used. The gas supply was blinded for all persons involved. The patients were put in two categories according to age and then randomly assigned to two groups with the patients breathing either oxygen or air at 2.5 ATA for 90 minutes 5 days per week for a total of 30 treatments (week 0 to week 6).

Evaluation

The wound area was copied onto transparent film covering the wounds first at 2 weeks before hyperbaric treatment, again when treatment was initiated (week 0), and at 2, 4, 6, and 18 weeks later. The wound area was read into a 386 computer by using a scanning device, and the wound area was then measured by using a specially made program (SAREA®). The calculations were not done until after completion of the study.

Statistics

Because two independent groups were used in the trial, the Mann-Whitney U test, table J, was used, and only the two-tailed results were examined.

Results

All patients went through the 30 treatments. No patient was hospitalized and no patient withdrew.

There were eight patients in each group. The median age in the group treated with oxygen was 71 years (range 75 to 45); in the group treated with air, the median age was 63 years (range 74 to 42). There were five males and three females in the oxygen group and three males and five females in the air group. Only one wound from each patient was included in the measurements (Table I).

The mean decrease of the wound areas at weeks 2, 4, and 6 in the oxygen group were 6.6 percent (SD $\pm$ 14), 22 percent (SD $\pm$ 13), and 35.7 percent (SD $\pm$ 17), respectively, and in the air group, 2.8 percent (SD $\pm$ 11), 3.7 percent (SD $\pm$ 11), and 2.7 percent (SD $\pm$ 11), respectively, 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 (Table II, Fig. 1).

TABLE I
Wound Area Matching Wounds*

	Patients							
	1	2	3	4	5	6	7	8
Week 0								
Air	221	268	437	500	528	1620	1864	1969
Oxygen	209	366	460	563	585	1587	1624	3070
Week 6								
Air	223	281	370	419	492	1696	1697	2273
Oxygen	77	135	321	433	418	1143	1164	2420

* Values expressed as millimeters squared.

TABLE II
Wound Area ($\bar{X}$) Expressed in Percentages

	Week −2	Week 0	Week 2	Week 4	Week 6
Air	101	100	97	96	97.3
Oxygen	99.3	100	93.4	78.2	64.3
	NS	NS	NS	$p < 0.05$	$p < 0.001$

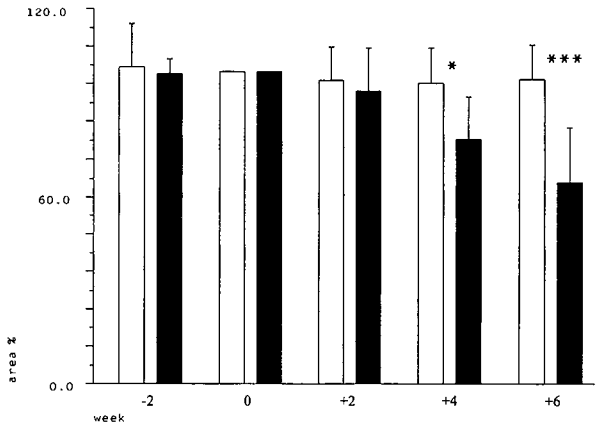

FIG. 1. Wound area (mean ± SD) expressed in percentages. * $p < 0.05$ at week 4, *** $p < 0.001$ at week 6, using the Mann-Whitney U test. □, air group; ■, oxygen group.

DISCUSSION

Hyperbaric oxygen treatment, given for 90 minutes per day at 250 kPa (2.5 ATA) for 5 days a week, had a significant effect on wound healing in the leg ulcers studied. There was a gradual response during the 6 weeks of chamber treatment, with the changes being significant from week 4.

Hunt[8] explained the role of oxygen in wound healing. Lactate synthesized by macrophages is the fundamental trigger stimulating fibroblasts to make collagen. Fibroblasts cannot synthesize collagen without a reasonable amount of oxygen, which is required for the post-translational processing of collagen necessary for its cross-linking space. There is a delicate balance of vessel growth and collagen deposition that is easily upset when host circulatory and nutritional support fail. Because macrophages release lactate, even while well oxygenated, some stimulus to collagen synthesis remains even during hyperoxygenation.

Oxygen breathing causes vasoconstriction and a flow reduction, as shown by Bird and Telfer.[9] They found a 20 percent flow reduction in limb circulation in humans during oxygen breathing but suggested that this vasoconstriction is well compensated for because of the increased amount of oxygen dissolved and transported in the plasma. Lindblom et al.[10] studied the influence of oxygen on perfused capillary density and capillary red cell velocity in rabbit skeletal muscle. They showed that closure of normal capillaries is probably related to the level of oxygen. Whether injured capillaries react in a similar way is unknown, although data from the research done by Perrins[3] suggest a positive effect of hyperbaric oxygen on the survival of split thickness skin grafts.

In a human study, Dooley and Mehm[11] found that hyperbaric oxygen at 2.0 and 3.0 ATA results in an increase in peripheral tissue O_2-delivery, despite vasoconstrictive reductions in peripheral (calf) blood flow.

Using a laser Doppler flowmeter, Hammarlund et al.[12] studied the effects of oxygen breathing on the dermal circulation in healthy volunteers. They found a dose-dependent vasoconstriction in skin in response to oxygen breathing. In a separate experiment, a patient with a chronic venous leg ulcer was tested. He responded to oxygen breathing with the expected vasoconstriction on the fingertip, but flow in the diseased skin near the ulcer remained unchanged. After successful treatment, the dermal vascular response to hyperoxia was normalized in the lower limb. The authors suggested that the dermal flow reduction observed in healthy volunteers is not a general reaction but rather a physiologic response to hyperoxia. Presence of the reaction might thus indicate that the inhaled oxygen has reached the tissues and caused hyperoxia.

Tensile strength of wounds, collagen deposition, and the rate of closure of a dead space are affected by the amount of available oxygen. The decrement due to hypoxia is significant, and so is the increment above normal with clinically obtainable hyperoxia. The increment relates to faster rather than excessive healing. This may seem paradoxical unless one accepts that hypoxic macrophages impel repair. When hypoxia is no longer a feature of the central dead space, healing stops and thus is not allowed to become excessive. Because angiogenesis is accelerated when extra oxygen is supplied by the circulation, healing is completed sooner.[8]

Giving the control group hyperbaric air meant that they were breathing 0.53 ATA oxygen when in the chamber; this was acceptable for the study in order to avoid the risk of the decompression sickness that would have arisen if a nitrox mixture containing 0.21 ATA oxygen

had been used. If the rise in oxygen partial pressure affected the wound healing, it would likely be in the same manner as in the oxygen group, with the differences shown between the two groups consequently smaller. There were no significant changes in wound areas in the control group, although minor changes were seen in some wounds (Table I).

Breathing in a closed mask system during hyperbaric treatment required more effort, despite well-functioning masks. However, using the laser Doppler technique, we have previously shown (unpublished data) the dermal microcirculation to be unaffected by breathing in the masks; i.e., there is no evidence of significant carbon dioxide retention due to breathing in the double masks.

Although five patients left the study at week 18 (three patients in the control group and two in the oxygen group), the remaining data indicate a continuing effect on wound healing after the hyperbaric treatment had ceased after week 6 (Table III), except in the largest wound, whose area returned to the initial value. During the period between week 6 and 18, two wounds healed that had initially measured less than 400 mm^2; in addition, a wound that had measured 460 mm^2 initially showed continued healing. In the control group, one wound started to heal after 6 weeks of hyperbaric treatment.

Study Design

Patients. In light of the results published by Slack[1] and Bass,[2] we decided that eight patients in each double-blind group (oxygen or air) would be sufficient to show significant changes in wound healing.

Besides the exclusion of a smoking habit, diabetes mellitus, or a large vessel disease, we assumed that extreme age might be an important factor. When looking at the age distribution of patients with chronic, nondiabetic leg ulcers seen at the department of surgery, Helsingborg Hospital, we found 12 patients with ranging from 45 to 81 years of age. Because of the age distribution, we decided to randomize to age <50 years or >50 but <75 years. The randomization made the two groups similar in age distribution. (One patient was younger than 50 years of age in each group, and the rest of the patients were between 50 and 75 years of age.)

Technical Arrangements. In the chamber room we had arranged two extra gas pipes to penetrate the chamber wall. These pipes were connected to the double mask systems inside the chamber, one marked "gold-gas" and the other marked "silver-gas." The gas supplies were blinded for all, except for a technician, who connected the gas pipes to the ordinary gas supply on the basis of a coin toss. A reduction valve reducing the air pressure to exactly match the oxygen pressure (4.5 bar) had to be included above the ceiling. Because of the double penetrations through the chamber wall we were able to treat "silver-gas" patients and "gold-gas" patients at the same time.

Procedures. We made up 16 envelopes containing instructions to put a patient on either "gold-gas" or "silver-gas" treatment. For two envelopes, marked "<50," we put an instruction of "gold-gas" in one and "silver-gas" in the other. In the remaining 14 envelopes, seven contained instructions for "gold-gas" and seven for "silver-gas." As patients entered the study, an envelope was drawn according to the two age groups and the patient was placed on the coded gas supply given by the instruction.

Entrance Rate. From the start, five patients were accepted after having met the inclusion criteria, and thereafter, two to three patients a year entered the study. Only patients living in Helsingborg who were being regularly treated at the department of surgery, the department of dermatology, or by general practitioners were included.

Conclusion

This double-blind study has shown a significant effect on the wound healing of nonatherosclerotic, nondiabetic chronic leg ulcers. The results indicate that hyperbaric oxygen

TABLE III

Wound Area Matching Wounds in Week 18*

	Patient							
	1	2	3	4	5	6	7	8
Air	292	–	–	42	309	1315	1652	–
Oxygen	0	0	–	103	–	816	1120	3027

* Values expressed as millimeters squared.

therapy might be used as a valuable adjunct to traditional therapy, including the grafting of leg ulcers, when conventional therapies have failed.

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Subject: Discussions with Dr Hammerlund
Date: Monday, 5 November 2012 23:32:27 AET
From: Hyperbaric Health - Dr Glen Hawkins
To: richard.bartlett@health.gov.au
CC: Tim Snowden - Hyperbaric Health

Dear Richard.

I have been in correspondence with Dr Christer Hammarlund (lead author of the RCT) over the weekend and he seems to believe that the paper (which was done as a confirmation paper to two other studies) was highly positive towards HBOT and can't work out why it has been interpreted any other way. He concedes that the 18 week data (which he intended to show the ongoing process of healing) confused the issue as it wasn't statistically analysed but the trend remained. That would place the interpretation in the same way that we discussed that its a positive paper for HBOT and should be interpreted as such from the author. That would imply that the only RCT is in favour of HBOT. Would this be considered as new information considering that the MSAC committee has used a completely different interpretation than the lead author?

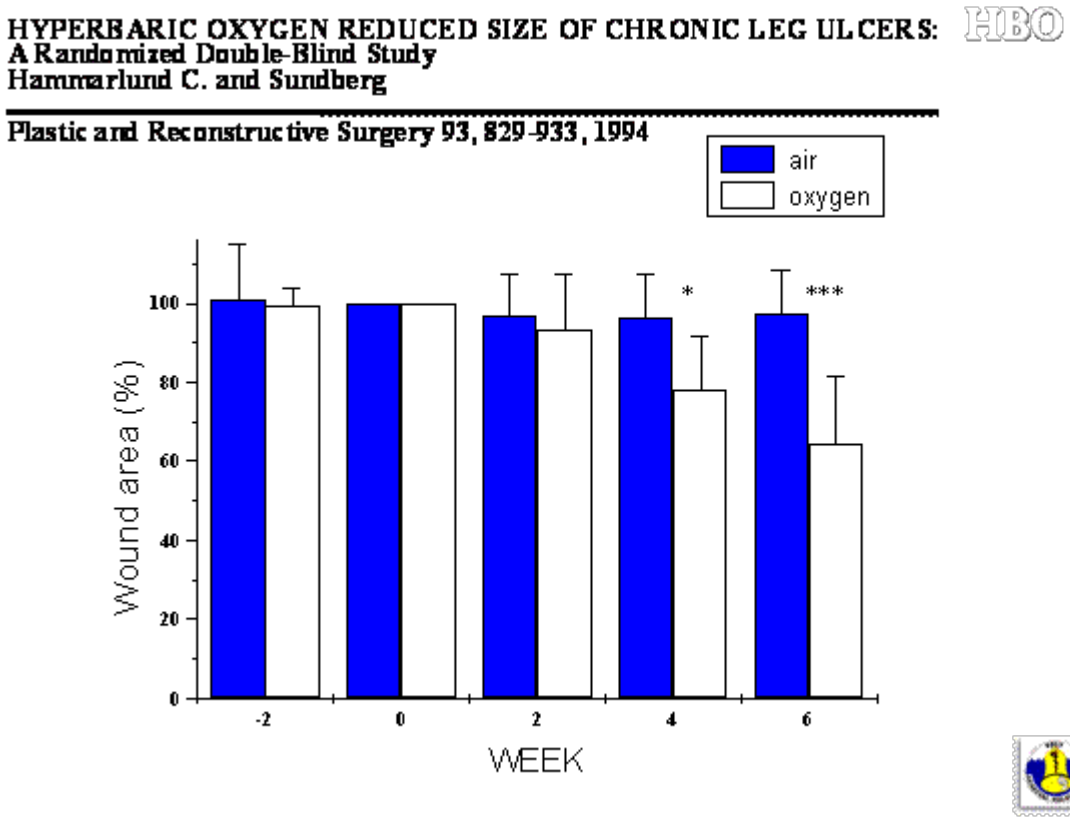
Regards Glen

FROM Christer Hammarlund.

Dear Dr Glen Hawkins

What you find enclosed below is a slide and my introduction during a European conference regarding wound healing in 2006.
I hope this information will help you.

The RCT from 1994 intended to answer if HBO could improve chronic wound healing – and it did!
- as you can see in the slide



Here I give you my introductory comments made during the conference:

Conference on oxygen and tissue repair
27-28 October 2006
Ravenna Italy

My talk had the title:
Role of HBO in the management of limb ulcer

1 2 3	INTRODUCTION Mister chairman, honoured colleagues! Mainly I intend to discuss my paper regarding the effect of HBO on chronic leg ulcers in otherwise healthy patients. I will also try to explain the basic mechanisms "why HBO works" in chronic and hypoxic wounds. This study was done because in 1983 I did not find any randomized controlled double blind study in the literature. As TK Hunt commented the study as a referee: this study has long been overdue.
4	30 HBO sessions in 6 weeks caused significant reduction of the wounds at week 4, and at week 6 in this randomized double-blind study (1).
	STUDY DESIGN The study was not designed to achieve healing of ulcers, just to confirm the effect of hyperbaric oxygenation in a chronic wound model. An earlier and open study by Bass (2) had shown that to heal 89 percent of similar wounds, the number of treatments ranged from 16 and up to 200 treatments, with a mean of 61. We used 30 treatments (90 minutes at 2.5ATA five days a week) in our study because of practical (and economical) reasons.
   5	TYPE OF PATIENTS In light of the results published by Bass we decided that eight persons in each double blinded group (air or oxygen) would be sufficient to show significant changes in wound areas. Thus sixteen, otherwise healthy patients, with chronic leg ulcers with a duration of more than 1 year were included. Patients with a smoking habit or concomitant chronic condition were excluded. The patients had no signs of large vessel disease in order to exclude arterial perfusion disturbances as a factor in the pathogenesis of the chronic wound. This was confirmed by measuring the distal blood pressure at the ankle and the first digit to be within normal limits - That leaves the pathology of the wounds mainly to consist of venous insufficiency.
6	RANDOMIZATION Because age itself might be a factor in problem wound healing we made the two groups similar in age distribution by randomize to age less than50 years or over50 but not over75 years. -

7	DOUBLE BLIND DESIGN The blinding of the treatment was arranged by two extra gas pipes to penetrate the chamber wall and were connected to the double mask system inside the chamber as "gold gas" and "silver-gas". These gas supplies were blinded to all but a technician, who connected the gas pipes to the ordinary gas supply above the ceiling on the basis of a coin toss. A reduction valve had to be inserted to reduce the air pressure to exactly match the oxygen pressure. As patients entered the study an envelope was drawn according to the two age groups and placed on the coded gas supply given by the instruction.
	WOUND MEASUREMENTS The patient's ordinary doctor and nurse were contracted to copy the wound area onto transparent film covering the wounds. This was done 2 weeks before the start of the hyperbaric treatment and 2, 4, 6 and 18 weeks later. The wound areas were then scanned into a computer. No calculations were made until after completion of the study. A specially made program that counted pixels was used to measure the wound areas.
	RESULTS IN DETAIL In the oxygen group there was an overall reduction in wound area after 30 HBO-treatments of 36% compared with 3% in the control group. Being carefully selected and otherwise healthy patients it is tempting to look at the matching wound areas. Just looking at the smaller wounds (up to 366 mm^2) the effect of HBO was a reduction of 63% because of 30 hyperbaric tretments. At follow up 3 months later these wounds had completely healed The larger wound areas showed less, but nonetheless significant effect with a reduction of 21-30%. Remember that a reduction in wound area of 10 to 15 percent a week represents normal healing as Attinger and coworkers stated this year, and this is how the smallest wounds reacted. Regarding the small number of treatments it is not a surprise that the larger wounds did not heal.

Looking forward to your comments

Best regards
Christer Hammarlund

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