Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of periwound transcutaneous oximetry as a predictor of wound healing response: A randomized prospective controlled trial

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Abstract

Background: Hyperbaric oxygen therapy (HBOT) is a treatment option for chronic nonhealing wounds. Transcutaneous oximetry (TCOM) is used for wound assessment. We undertook a randomized prospective controlled trial to evaluate the role of HBOT in healing of chronic nonhealing wounds and to determine whether TCOM predicts healing.

Materials and Methods: This study was conducted in 30 consenting patients with nonhealing ulcer. The patients were randomized into group HT (receiving HBOT in addition to conventional treatment) and group CT (receiving only conventional treatment). Duration of treatment in both the groups was 30 days. Wound ulcer was analyzed based on size of the wound, exudates, presence of granulation tissue, and wound tissue scoring. Tissue oxygenation ($TcPO_2$) was measured on 0, 10th, 20th, and 30th day.

Results: There was 59% reduction in wound area in group HT and 26% increase in wound area in group CT. Ten patients in group HT showed improvement in wound score as compared to five patients in group CT. Complete healing was seen in three patients in group HT as compared to none in group CT. Surgical debridement was required in 6 patients in group HT and 10 patients in group CT. One patient in group HT required amputation as compared to five patients in group CT. A positive correlation was found between $TcPO_2$ value and various markers of wound healing.

Conclusion: HBOT has a definitive adjunctive role in the management of chronic nonhealing ulcers. It decreases the amputation rate and improves patient outcome. Periwound $TcPO_2$ may be used as a predictor of response to HBOT and has a positive correlation with wound healing.

Key words: Hyperbaric oxygen therapy, nonhealing wounds, transcutaneous oximetry

Introduction

Chronic nonhealing wound are common and have a high impact on the well-being of those affected.[1] They are often associated with diabetes mellitus, arterial, and venous disease. Increased oxygen demand, requiring sufficient supply of blood, is there during ulcer healing.[2] Hyperbaric oxygen therapy (HBOT) is a systemic treatment option, wherein a patient breathes pure oxygen at greater than one atmospheric pressure for a specified period of time. Therapeutic effects of HBOT are due to an increase in dissolved oxygen in plasma and tissue oxygen delivery. At 2.5 absolute atmosphere (ATA), partial pressure of oxygen (PaO_2) increases from 760 mmHg at room air to 1900 mmHg, on breathing in 100% oxygen, and the plasma content of oxygen increases from 0.3 to 5.62 volume-percent. HBOT promotes healing in chronic nonhealing wounds by means of its antiedema effect, augmenting neovascularization, stimulating fibroblast proliferation and differentiation, increasing collagen formation and cross linking, and stimulating leukocyte microbial killing.[2-4] Although HBOT has gained popularity as an adjunctive treatment for

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problem wounds, there are only few randomized controlled studies that support its efficacy.

Transcutaneous oximetry (TCOM) is a simple, reliable noninvasive technique for the objective assessment of wound perfusion and oxygenation.[5] Its definitive role in predicting the wound healing has not yet been proven. We undertook a randomized controlled trial to evaluate the role of HBOT in healing of chronic nonhealing wounds and to determine whether TCOM predicts healing.

Materials and Methods

This prospective randomized controlled study was conducted after the approval of the institutional research and ethical committee. Patients referred from surgical specialties to the hyperbaric oxygen unit of the Department of Anaesthesiology, with the complaint of chronic nonhealing ulcer, were included in the study. Patients in the age group of 18–65 years of either sex with a nonhealing ulcer, despite conventional therapy of more than 4 weeks duration, were included in the study. Patients who were not willing for HBOT, those with active upper respiratory tract infection, with any active lung pathology or pregnancy were excluded from the study. Written informed consent was obtained from all the patients.

Investigations including complete hemogram, random blood sugar, electrocardiogram, and X-ray chest were reviewed. Duration of wound, associated medical illness including history of smoking, diabetes mellitus (DM), hypertension (HTN), and the type of treatment received and advised were recorded. Ear, nose, throat examination was performed by an Otorhinolaryngologist to rule out upper respiratory tract infection and inflammation of tympanic membrane. Local examination of the wound was done and the size (length and width), number, site, color of the surrounding skin, type of wound, discharge, vascular insufficiency, or associated varicose vein were recorded. Doppler examination was performed to confirm vascular insufficiency.

Thirty consenting patients were randomized by computer-generated random numbers into two groups. Group HT patients received HBOT in addition to conventional treatment, while Group CT patients received only conventional treatment. Duration of treatment in both the groups was 30 days. All the patients received conventional therapy for the management of wounds, i.e., wound debridement, treating infection, daily dressing, etc., which was managed by the referring surgeon. In group HT patients, HBOT was administered at 2.5ATA in a "monoplace" chamber [Bara-Med monoplace hyperbaric chamber, Biomedical systems, Environmental Tectonics Corporation, Southampton, PA, USA) for 90 min, 6 days a week. A total of 30 sessions were administered to each patient along with conventional treatment.

Wound ulcer was analyzed on 0, 10th, 20th, and 30th day and assessment of healing in both the groups was performed on the basis of size of the wound [area of wound (sq cm) was obtained by product of the greatest length (cm) and greatest width (cm)], exudates (an estimate of ulcer was assessed on the presence or absence of exudates), presence of granulation tissue and wound tissue scoring [the wound (ulcer) bed was scored on a score of 0–4] [Table 1].

TCM 400/TINA using Miniature Clark electrode (Tina TCM 400 Transcutaneous pO_2 monitoring system, Radiometer Copenhagen, Bronshoj, Denmark) was utilized for measuring tissue oxygenation ($TcPO_2$) in all the patients of both groups. Measurements were recorded on noninflammed skin 1 cm proximal to the upper margin of ulcer. $TcPO_2$ values were recorded on 0, 10th, 20th, and 30th day. TcPO2 was measured by an electrochemical transducer, which was fixed to the skin with the help of an adhesive ring and contact liquid supplied by the manufacturer. The measuring site was cleaned carefully by a disinfectant (chlorhexidine-spirit). The skin oxygen partial pressure was determined by measuring the oxygen reduction current by means of a measuring cell. To increase the permeability of the skin to oxygen molecules at the measuring site, the transducer is heated to 44°C. The calibration period was on an average 10 min, and the $TcPO_2$ signal was continuously recorded.

Patients requiring surgical debridement/amputation were noted. Any side effects related to HBOT were also noted.

Statistical analysis

The primary outcome variable was the wound size. Sample size of 30 patients was based on the predicted difference of 25% in the wound area in the two groups of treatment modality. Data were analyzed using SPSS Version 15.0. For quantitative variables, student *t*- test for independent samples was applied to test the difference amongst the averages of the quantitative data of the two groups. Paired *t*-test was applied to compare the difference between the means. For qualitative data, the chi square test, Fischer exact test, and Wilcoxon signed rank test were applied to test the difference amongst the two groups. Kendall's tau b test was applied for correlating periwound $TcPO_2$ with various parameters of wound healing. Nonparametric Mann Whitney U test was applied for comparing duration of wound as it had non Gaussian distribution.

Results

Forty-six patients were recruited for the study but only 30 patients fulfilled the study criteria and were randomized in the two groups (Figure 1 consort chart). All patients completed the study period and no patient was excluded from the study analysis. The demographic profile was comparable in the two groups [Table 1]. Both the groups were comparable in terms of comorbid conditions [Table 2]. Of the comorbidities, three patients had both DM and HTN and another three patients had DM, HTN, and were smokers. Common sites of wound were mid-foot (8 patients), leg (7 patients), fore-foot (6 patients), great toe (5 patients), other toes (1 patient), and other sites (3 patients).

There was 59% reduction in wound area (median baseline area of 24 cm^2 decreased to 6 cm^2 at 30 day of therapy, $P = 0.012$) in group HT and 26% increase in wound area (median baseline area of 16 cm^2 increased to 20 cm^2 at 30 day of therapy, $P = 0.221$) in group CT. This difference in the two groups was statistically highly significant ($P = 0.001$). Exudate resolved in 11 patients in group HT as compared to 3 patients in group CT ($P = 0.001$). There was significant improvement in exudates in group HT ($P = 0.006$) as compared to group CT ($P = 0.250$) from baseline exudates in the respective group. Granulation tissue appeared in 12 out of 15 patients in group HT as compared to 6 out of 15 patients in group CT ($P = 0.02$).

A significant improvement in wound score was observed in group HT as compared to group CT after 20 days of treatment [Table 3]. Significant improvement in wound score was observed after every 10 sittings of HBOT in Group HT [Table 4]. After 30 days of treatment in both the groups, 10 patients out of 15 in group HT ($P = 0.006$) showed improvement in wound score (decrease in tissue grade) as compared to 5 out of 15 patients in group CT ($P = 0.52$). Complete healing was seen in 3 out of 15 patients in group HT as compared to none in group CT after 30 days ($P = 0.07$). Surgical debridement was required in 6 out of 15 patients in group HT and 10 out of 15 patients in group CT ($P = 0.14$). One patient in group HT required amputation as compared to 5 patients in group CT ($P = 0.06$).

Table 1: The wound (ulcer) bed scoring

Score	Tissue type in the wound (ulcer) bed	Description
4	Necrotic tissue (eschar)	Black, brown or tan tissue that adheres firmly to the wound bed or ulcer edges and may be either firmer or softer than the surrounding skin.
3	Slough	Yellow or white tissue that adheres to the ulcer bed in strings or thick clumps or is mucinous.
2	Granulation tissue	Pink or beefy red tissue with a shiny, moist, granular appearance.
1	Epithelial tissue	For superficial ulcer, new pink or shiny tissue skin that grows in from the edges or islands on the ulcer surface.
0	Closed/resurfaced	The wound is completely covered with epithelium (new skin).

Table 2: Patient characteristics

Parameters	Group HT ($n = 15$)	Group CT ($n = 15$)	P value
Age (years)	46.9 ± 11.8*	47.4 ± 12.5*	0.91
Sex (M/F)	12/03	13/02	0.78
Comorbidities			
Diabetes mellitus	5	5	1
Hypertension	6	6	1
Varicose vein	2	2	1
Vascular insufficiency	2	2	1
Smoking	7	6	0.71
Wound duration (months), median (range)	2 (1–60)	2.5 (1–36)	0.6

Values are expressed as mean + standard deviation

Table 3: Assessment of wound tissue score

Tissue grading (Grade 0: 1: 2: 3: 4)	Group HT ($n = 15$)	Group CT ($n = 15$)	P value
Baseline	0:0:5:7:3	0:1:1:9:4	0.25
On 10th day	0:3:8:3:1	0:1:3:8:3	0.08
On 20th day	0:7:5:2:1	0:0:5:6:4	0.01
On 30th day	2:6:4:1:2	0:0:6:3:6	0.02

Table 4: Comparison of wound tissue score from baseline at different time intervals of therapy

	Improvement in wound score (n)	No change in wound score (n)	Deterioration in wound score (n)	P value
Group HT ($n = 15$)				
After 10 days	9	6	0	0.005
After 20 days	10	5	0	0.004
After 30 days	10	4	1	0.006
Group CT ($n = 15$)				
After 10 days	3	12	0	0.08
After 20 days	5	9	1	0.31
After 30 days	5	8	2	0.52

After 30 days, periwound $TcPO_2$ (at room air) improved by 11.8 mmHg in group HT ($P = 0.01$) and decreased by 5.7 mmHg from baseline value in group CT ($P = 0.2$) [Table 5]. On monitoring periwound $TcPO_2$ at regular intervals in both the groups, an increasing trend in $TcPO_2$ values were observed in group HT ($P = 0.09$ at 10 days, 0.008 at 20 days, and 0.012 at 30 days as compared to baseline), while a falling trend was observed in group CT ($P = 0.68$ at 10 days, 0.49 at 20 days, and 0.22 at 30 days as compared to baseline).

A positive correlation was found between $TcPO_2$ value and various markers of wound healing, such as decrease in area of the wound, decrease in exudate amount, and improvement in wound score [Table 6]. A negative correlation was found between $TcPO_2$ value and amputation rate. Periwound $TcPO_2$ values were monitored at regular intervals in both the groups and a positive correlation was found between $TcPO_2$ values and various markers of wound healing, such as decrease in area of the wound ($P = 0.004$), decrease in exudate amount ($P = 0.001$), and improvement in wound score ($P = 0.01$). A negative correlation of 0.53 was found between $TcPO_2$ values and amputation rate ($P = 0.004$). Higher the periwound $TcPO_2$ levels, lesser is the amputation rate ($P \leq 0.05$). Higher the periwound $TcPO_2$ levels more are the chances of wound healing. Individually, correlations were significant in group HT and not in group CT.

Common adverse effects seen with HBOT were pressure related ear discomfort/pain (3 patients), claustrophobia (2 patients), headache (1 patient), and tinnitus (1 patient).

Table 5: Periwound $TcPO_2$ values

	Group HT ($n = 15$)	Group CT ($n = 15$)	*P* value
Baseline	22.5 ± 13.4	27.1 ± 15.9	0.407
Day 10	28.1 ± 17.2	25.9 ± 10	0.663
Day 20	33.3 ± 18.5	24.7 ± 9.9	0.122
Day 30	34.3 ± 14.8	21.4 ± 9.5	0.008

Discussion

We found that HBOT helps in nonhealing ulcer by decreasing exudate and promoting granulation tissue. The wound size decreases and wound tissue type is improves. A positive correlation was found between $TcPO_2$ values and various markers of wound healing, such as decrease in area of the wound, decrease in exudate amount, and improvement in wound score. A negative correlation was found between $TcPO_2$ values and amputation rate.

Our results are in agreement with other studies showing positive effects of adjunctive HBOT on chronic non healing ulcer. Oriani *et al.*, Zamboni *et al.*, Faglia *et al.*, Baroni *et al.*, and Kalani *et al.* reported better healing and lower amputation rate after HBOT as compared to conventional therapy in patients with nonhealing ulcer.[6-11]

Measurement of TcPO2 during inhalation of pure oxygen or HBO exposure has been used to select patients for HBOT[10] and values under 40 mmHg were associated with poor ulcer healing in diabetic patients.[12] Diabetic patients with local hypoxic foot ulcer (TcPO2 < 40 mmHg) benefit from HBOT when TcPO2 value increases to >100 mmHg and/or at least three times basal value during inhalation of pure oxygen.[10] $TcPO_2$ measured in chamber under hyperbaric conditions provides the best single discriminator between success and failure of HBOT, using a cut-off score of 200 mmHg.[13] These data supported the use of in-chamber $TcPO_2$ as a screening tool.[14] HBOT may be added to conventional treatment of diabetic foot ulcers if periwound $TcPO_2$ in 2.5 ATA HBO is over 200 mmHg.[14] In our study, periwound $TcPO_2$ levels at room air were also monitored in both the groups in order to assess the role of $TcPO_2$ in predicting wound healing. Periwound $TcPO_2$

Table 6: Correlation of periwound $TcPO_2$ and various parameters of wound healing

Group	Improvement in $TcPO_2$	Improvement in tissue grading (decrease in wound score)	Improvement in exudates (decrease in exudates)	Change in wound size (decrease in wound area)	Amputation rate
Total ($n = 30$)	Correlation	0.473*	0.675**	0.535**	-0.535**
	Coefficient significance (2-tailed)	0.011	0.001	0.004	0.004
Group HT ($n = 15$)	Correlation	0.612*	0.739**	0.784**	-0.535*
	Coefficient significance (2-tailed)	0.022	0.006	0.003	0.046
Group CT ($n = 15$)	Correlation	0.213	0.294	-0.237	-0.426
	Coefficient significance (2-tailed)	0.425	0.271	0.376	0.111

**Correlation is significant at the 0.05 level (2-tailed)., **Correlation is significant at the 0.01 level (2-tailed)*

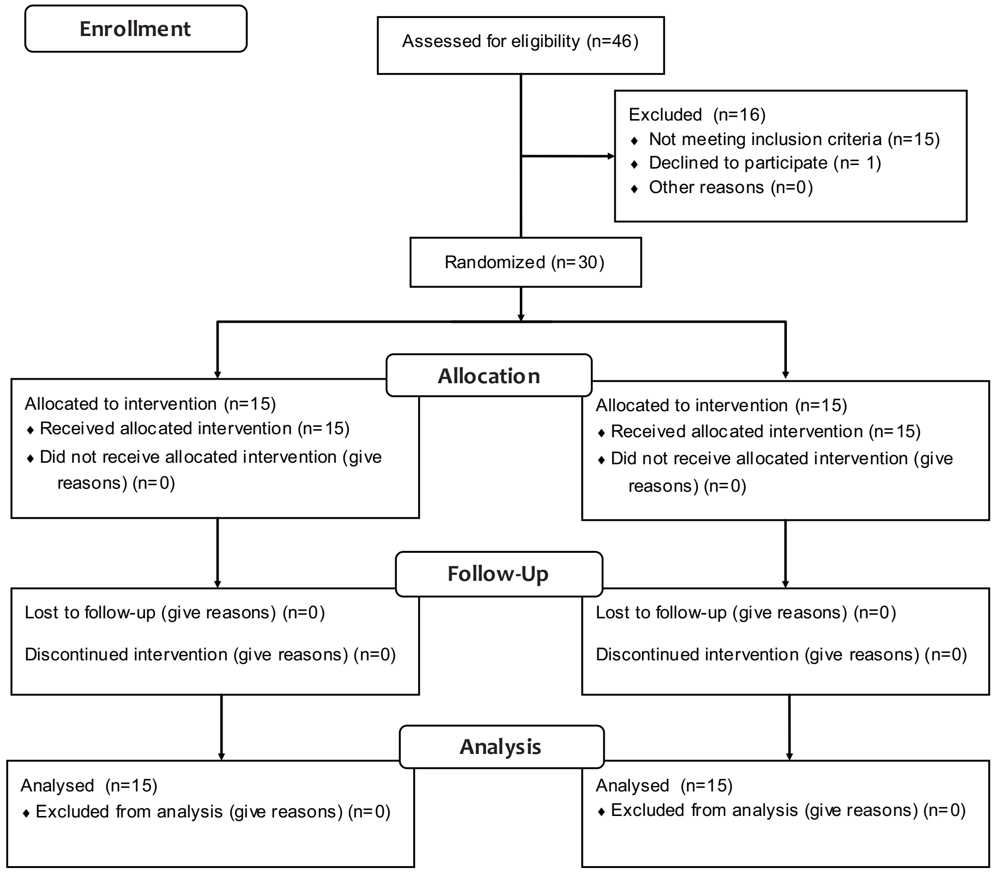

Figure 1: Consort chart

levels were also measured inside the chamber in group HT and the highest reading inside the chamber was recorded. Wyss *et al*. measured $TcPO_2$ in patients with wounds and found an increasing probability of failure with decreasing $TcPO_2$.[15] We also found a positive correlation between $TcPO_2$ values and various markers of wound healing, while a negative correlation of 0.53 was found between $TcPO_2$ values and amputation rate. Initial (room air) TCOM values do not predict outcome however patients who go on to heal have a higher TCOM value after breathing 100% oxygen than those who do not heal.[16] Better results can be obtained by combining information about sea-level air and in-chamber oxygen measurement.[13] A sea-level air $TcPO_2$ <15 mmHg combined with an in-chamber $TcPO_2$ < 400 mmHg predicts failure of HBOT. Only one patient in our study had in-chamber $TcPO_2$ < 400mmHg and this patient (from group HT) had vascular insufficiency. He did not respond to treatment and had to undergo amputation. Statistical significance of this could not be calculated, and therefore, we cannot comment upon the in-chamber $TcPO_2$ values as a predictor of response.

10 out of 15 patients in group HT showed signs of healing compared to 5 out of 15 patients in group CT which corroborates with the findings of the study by Kalani *et al*.[10]

Complications reported in patients treated with HBOT include ear pain (17%) and generalized seizures (0.5%).[17] In our study, the most common adverse effect with HBOT was pressure related ear discomfort/pain (20%), followed by claustrophobia (13%). No cases of seizure or pneumothorax were observed in our study.

The limitations of our study were that long-term impact of HBOT on wound healing was not studied beyond 30 days and that we included patients having ulcers due to different causes. However, the two groups were comparable.

We conclude that HBOT has a definitive adjunctive role in the management of chronic nonhealing ulcers. Problem wounds require multidisciplinary, aggressive, and a combined approach including administration of HBOT. Administration of HBOT along with conventional treatment decreases the amputation rate and improves patient outcome. Periwound $TcPO_2$ values may be used as a predictor of response to HBOT and have a positive correlation with respect to wound healing. No serious adverse effects have been observed with HBOT.

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