ORIGINAL ARTICLE

Use of hyperbaric oxygen therapy (HBOT) in chronic diabetic wound - A randomised trial

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ABSTRACT

Introduction: The purpose of this study was to investigate the effect of hyperbaric oxygen therapy (HBOT) towards diabetic foot ulcer (DFU) patients in addition to the standard wound care management.

Methods: Fifty-eight diabetic patients with ulcers at Wagner Grade 2 and above involved in this study after presented at two study centres of tertiary teaching hospitals. The assigned patients received conventional wound care with additional HBOT given at 2.4 ATA for 90 minutes. Patients in the control group who received conventional wound care only were treated and observed for 30 days. The progress of wound healing was observed and measured at day 0, 10, 20 and 30 of study. The data collected were analysed using SPSS software (ver. 22) to study the association of HBOT towards healing of the diabetic foot ulcers.

Results: Repeated Measures ANOVA analysis with Greenhouse-Geisser correction indicated that the means of wound size over time points (Day 0, 10, 20 and 30) among patients under HBOT group were statistically significantly different [$F(1,61)=30.86$, $p<0.001$)] compared to conventional therapy group. Multiple logistic regression analysis showed that HBOT group has nearly 44 times higher odds to achieve at least 30% wound size reduction within the study period (95%CI: 7.18, 268.97, $p<0.001$).

Conclusion: The results obtained in this study indicated that as an adjunctive therapy to conventional wound care, HBOT affected the rate of healing in diabetic foot ulcers significantly in terms of wound size reduction when compared to administering the conventional wound care alone.

INTRODUCTION

According to the National Diabetes Registry Report (NDRR), the prevalence of diabetes mellitus among Malaysian of more than 30 years old has increased by more than two-folds over a 20-year period, i.e., from 6.3% to 14.9% between the years of 1986-2006. This is supported further by the NDRR that Malaysia has experienced an increase of 31% in diabetes prevalence as of the recent 2013.[1] Diabetes complications can affect various parts of the body and manifests in different ways. Serious complications may result such as renal disease, stroke and ischemic heart disease.[2] Diabetes foot ulcers (DFU), one of the common complications of diabetes is typically linked to lower extremity amputations in the industrialised world.[3]

DFU is characterised by slow or poor healing, partial or full thickness wound located distal to the ankle in a patient with diabetes mellitus.[4] It is usually recalcitrant to treatment and often associated with lower limb amputation as well as other medical complications. The median time to healing without surgery is of the order of 12 weeks, and they are associated with a high risk of limb loss through amputation. At best up to 77% of DFU patients sustain good wound healing but the remaining proportion represents a group unlikely to heal and who will live with a non-healing wound or undergo amputation.[5,6] Although DFU may seem superficial, microorganisms can spread to the subcutaneous tissues and if not properly treated may worsen the condition.[7] Standard management of DFU usually includes debridement, infection control, non-weight bearing and the use of dressings to maintain moist wound bed.[8] Despite the use of standard management strategies, the healing of DFUs remains a challenge for both the patients and medical practitioners.[9] In the recent years, hyperbaric oxygen therapy (HBOT) has been widely utilised as an adjunctive therapy to treat DFUs. Based on the scientific studies in the recent years, HBOT was found to facilitate wound healing to achieve an improved quality of life, when combined with the conventional wound management.[10] In all studies, HBOT was used as adjunctive therapy in addition to the standard treatment modalities of wound debridement and antibiotics. Nevertheless, there is not many reference on predictive factors of DFU wound healing among patients receiving mix therapy. There is also lack of data on temporal effects of HBOT on wound healing among DFU patients.[11] We hope that the information and results gathered in this study will give some indication about how HBOT affects the wound healing in DFU and how it may be of use in the management of DFU among Malaysian patients. In particular the investigators would like to determine the temporal effects of the HBOT compared to the conventional therapy and specifically to search for predictive factors of robust diabetic wound healing among patients receiving the HBOT.

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MATERIALS AND METHODS

Study design & subjects

This randomised trial was conducted in 2014 in two tertiary centres and one private hyperbaric healthcare facility. The primary endpoint of the study was to compare the effect of HBOT as an adjunctive therapy to conventional wound management in a group of non-healing diabetic wounds in the study group (HBOT) versus the conventional treatment. Investigation was done based on the physiological and clinical parameters of the wound site (Figure 1). The overall methodology and the study design of this research consist of two arms comparison namely treatment and control groups that utilised a pre-determined statistical values (alpha 0.05; power 80%; ratio 1; delta 20%). The randomisation was carried out at the study centre by using sealed envelopes. Sample calculated inclusive 10% drop-out was 28 patients for each group.

Inclusion & exclusion criteria

In this study diabetes patients with foot ulcers in their lower extremities were recruited. The non-healing is considered when the wound was treated at the study centres for more than thirty days and failed to achieve wound size reduction of more than 30%.

Patients selected were presented with DFU of Wagner scale 2 and above.[12] It comprised of ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis; deep ulcer with abscess, osteomyelitis, or joint sepsis; gangrene localised to portion of forefoot or heel and extensive gangrenous involvement of the entire foot. However, the investigator did not categorise further treatment effects for the selected patients with the scale 2 and above. The eligible patients for this study were determined based on the inclusion and the exclusion criteria as detailed below. All patients selected in the study group were presented with problematic diabetic foot ulcer and underwent the transcutaneous oximetry measurement with oxygen challenge. In this study, the desired $TcpO_2$ value was at least 20mmHg. However, exceptions were made to $TcpO_2$ values that increased by at least 50% after oxygen challenge. The $TcpO_2$ test would have indicated patients with chronic wound who still had acceptable peripheral perfusion to lower limb tissues. This would also rule out those patients with peripheral vascular disease with very poor peripheral perfusion. All patients underwent laboratory test procedures for fasting blood sugar, HbA1c, renal function test and daily pre-treatment capillary blood sugar. Other investigations included chest X-ray and electrocardiogram. Results of pre-treatment wound culture, any other associated medical illness, history of smoking, hypertension and duration of wound were also noted. Ear, nose and throat examination were performed to rule out upper respiratory tract infection and inflammation of tympanic membrane.

Any conditions contraindicated for HBOT were excluded (e.g., pneumothorax, emphysema, chemotherapy, middle ear disease and upper respiratory infection). Patients with ulcers that have been amputated and/or treated with other adjunctive therapy that included topical hyperbaric, honey wound dressing, maggot therapy as well as pre-exposure to hyperbaric oxygen, were excluded. Further, the usage of recombinant or autologous growth factor products, skin and dermal substitutes within the past 30 days were also excluded. Simple randomization method was carried out by the referring physician using an opaque envelope containing indicators of group A and B. Envelope A referred to standard wound care and HBOT while envelope B to standard wound care only.

Treatment procedures

Participants in this study all received standard conventional wound care regime that included wound cleansing, wound dressing and wound debridement. Whenever present, wound infections were treated with medications.

Review and evaluation of the wounds were carried out after 10th, 20th and 30th treatment during the study duration. Evaluation was done by direct observation, photographing and measuring of wound size by area of wound (cm^2) from the greatest length (cm) and greatest width (cm). Measuring of oxygen tension value in the peri-wound area with the transcutaneous oximetry machine (Tina TCM30 Transcutaneous P_aO2 monitoring system, Radiometer Copenhagen, Denmark) was done and repeated on day 15th and 30th of study.

Patients in the HBOT group received conventional wound therapy with hyperbaric oxygen treatments at 100 percent concentration of 2.4 atmospheres absolute (ATA) as an adjunctive therapy. This treatment was performed daily from Mondays to Fridays for thirty sessions. Patients underwent a hyperbaric treatment of 90 minutes in each session in a mono-place hyperbaric chamber (Series III®, San Diego, California and Baramed®, ETC©, USA).

Data analyses

The data collected in this study was analysed using the Statistical Package for Social Sciences (SPSS) software version 20. Chi-square (χ^2) test was used to compare the sociodemographic characteristics and variables for categorical values, independent t-test was performed for numerical values. The observed primary outcome was the mean wound size in cm^2. Time or temporal effect within the subjects were studied by using repeated measure ANOVA to find the difference of mean wound size within the HBOT or control group based on time. Treatment effect between the subject groups on the other hand was aimed to find the difference of mean wound size between the two treatments group based on time. Multivariate Logistic Regression analysis was performed to the model for the associated factors that predict the robustness of wound healing in DFU patients from both treatment groups. P value of 0.25 was taken as cut off value for simple logistic regression analysis and hence variable selection for multivariate logistic regression. The independent variables chosen for the univariate logistic regression analyses include gender, duration of DM, smoking cigarette, HBA1c level, HBOT intervention, total white cell count, presence of renal impairment and duration of DFU. The use of both repeated measure ANOVA and multivariate logistic regression will minimise the confounder effects on the analysis. Robustness consideration was set at 30% based on investigator expert clinical opinions and study carried out by Sheehan et al.[13]

RESULTS

Sixty two (n=62) patients with type I and II diabetes with chronic diabetic ulcer were identified. Four of them were excluded from final data analysis due to insufficient data and premature withdrawal from the study (unavailable to contact via telephone and email). A total of 58 patients completed the study within the study period inclusive of follow up 30 days post treatment. Table I shows the comparison of demographic data of the intervention and control groups. Table II show the analysis of Within-Subject Effects (time effects) of Repeated Measures ANOVA to determine an overall significant between the means of wound size (cm^2) for both HBOT and control groups at different time points. Repeated Measures ANOVA with Greenhouse-Geisser correction shows means of wound size over time points (Day 0, 10, 20 and 30) among patients under HBOT group were statistically significantly different [$F(1,61)=30.86$, $p<0.001$)]. Based on the plots, the trend of wound size reduction for the HBOT group appeared to decrease more profoundly over time compared to the control group. (Figure 2)

Based on the univariate logistic regression analysis and clinical experience, the investigators included the HBOT, duration of foot ulcer prior to treatment and wound size at baseline into final model for the multivariate logistic regression analysis to search for predictors for robust wound healing (>30% wound size reduction). A DFU patient undergoing standard wound care with HBOT as an adjunctive treatment has nearly 44 times higher odds to achieve at least 30% wound size reduction within the study period, adjusting the baseline wound size and DFU duration with area under the ROC curve of 96%. Additional analysis also showed that an increase of $1cm^2$ in wound size at baseline could reduce the odds of wound healing by 3%. (Table III)

DISCUSSION

Problematic wound is a source of major concern for diabetics due to high risk of developing serious limb complications. Multiple factors can be involved in non-healing lower extremity ulcers in diabetes patients such as age, gender, habitual actions that includes diet and lifestyles.[14,15] HBOT has been used for the treatment of wounds for over two decades.[16] The rationale for this is related to the nature of hypoxia of ischemic wound and how hyperoxygenation can overcome this issue during HBOT. One of crucial effects of HBOT is an increase in angiogenesis activity that leads to formation of new blood vessels and hence increase in nutrients supply to the hypoxic tissue.[17,18] Subsequently, partial pressure of oxygen will be elevated in significant amount which leads to increase in dissolved oxygen in the arterial blood.[19] Oxygen is a prerequisite for wound healing that results in enhancement of reparative processes such as cell proliferation, bacterial defence, angiogenesis and collagen synthesis.[20] With the increase in the knowledge about the role of hyperoxia in wound healing process, more interest is seen in HBOT research as it reverses hypoxia and re-establishes the wound oxygen gradient.

In this study, the investigators have demonstrated that HBOT at 2.4 ATA for 90 minutes affected the wound healing in diabetes foot ulcer (DFU) patients and it does so favourably compared to conventional wound management alone as seen in trend of wound size reduction. The result in the multivariate logistic regression model demonstrated that treatment group as categorical variable is the strongest predictor of robust wound healing, thus suggesting that an individual with DFU undergoing HBOT have a higher chance in wound healing compared to individuals who received conventional therapy alone. This suggests that wound treated in the HBOT group experienced a more effective angiogenesis stimulation that enhanced wound healing. The finding in this study seemed to agree with studies performed by Abidia et al., and Kalani et al.[21,22] HBOT does not only increase oxygenation of the hypoxic wound tissues and enhanced the neutrophil-killing ability, but it also improves wound metabolism by means of collagen synthesis and in doing so speeds up the wound healing.[23] Wound healing process becomes impaired by low oxygen tensions, in particular when the partial pressure of O_2 is reduced below than 30mmHg.[24] As oxygen has both biochemical and vascular effects in our body, HBOT is aimed to provide intermittent correction of wound hypoxia. Partial pressures of oxygen is increased during HBOT and will act as a driving force for oxygen diffusion. This readily available oxygen within the periphery of hypoxic tissues allows for adequate reversal of the hypoxic tissue.[25,26] HBOT appeared effective in problematic diabetic ulcer by promoting the tissue granulation. In the recovery phase, the presence of newly divided fibroblasts is required for the development of granulation tissues and epithelialization.[27] This was noted in the reduction of wound area as the wound improved. This study supported the concept of adjunctive HBOT to enhance the healing of foot ulcers in diabetic patients.

Strikingly this study has shown that not only the HBOT results in significant wound size reduction, it also has a much faster effect on wound healing process compared to conventional therapy. The rationale that HBOT aids healing process may also be attributed to its ability to reduce local tissue edema by means of vasoconstriction of arterial vessel induced by increased oxygen content without compromising the supply of oxygen that is being dissolved in the plasma.[28,29] Subsequent to this, diffusion distance of oxygen from the vasculature to wound tissue increases together with the oxygen tension in the hypoxic wounds. In essence, oxygen diffuses more across the barriers created by hyperoxic vasoconstriction phenomenon. Many other advantages of HBOT on DFU wound have been described in the literature which was not covered by this research due to focus on the rate of healing as the main objective. Oriani et al., performed a prospective, non-randomised controlled trial on 80 patients. The endpoint of this study was the avoidance of amputation that was noted in the HBOT group (96%) versus the controlled group (67%).[30] Another six studies in the literature review has indicated that patients with DFU complicated by surgical infection, HBOT reduces odds of amputation (odds ratio, OR: 0.24, 95% confidence intervals, 95%CI: 0.14, 0.43) and improves chance of healing (OR 9.99, 95%CI: 3.97, 25.13). There is a high level of evidence that HBOT reduces risk of amputation in the DFU population by promoting partial and full healing of problem wounds.[31]

Table I: General demographic comparison between the intervention (HBOT) and control groups

Characteristics	HBOT Group		Control Group		P-value
	n (%) 29 (50%)	Mean (SD)	n (%) 29 (50%)	Mean (SD)	
Age (Years)		54.41(10.42)		57.97(11.47)	0.189[a]
Gender					
Male	10 (34.5)		19 (65.5)		0.018[b]
Female	19 (65.5)		10.(34.5)		
Smoking					
Smoking	7 (24.1)		7 (24.1)		
Non- smoking	22 (24.9)		22 (74.9)		1.000[b]
Renal Impairment					
Yes	2 (6.9)		3 (10.3)		1.000[b]
No	27 (93.1)		26 (89.7)		
Wound Size at Baseline (cm^2)		29.86(27.02)		24.49 (32.61)	0.861[a]
TcpO2 (MmHg)		36.72(7.19)		32.93(8.17)	0.228[a]
HbA1c (%)		9.88(2.41)		9.60 (2.48)	0.948[a]
Total White Cell count (109 per L)		11.97(4.81)		12.53 (5.69)	0.168[a]
DFU Duration (weeks)		6.31(15.06)		5.00(7.79)	0.667[a]

a Independent t-test
b Chi-square (χ^2) Fisher Exact's test

Table II: Post Hoc comparison of wound measurement (cm^2) within each treatment groups based on time (Time Effects)

Comparison	HBOT Group mean diff. (95%CI)	Control Group p-value	mean diff. (95%CI)	p-value
Day0-Day10	7.39 (2.09, 2.69)	0.003	0.60 (-0.12, 1.32)	0.149
Day0-Day20	11.85 (5.96, 17.74)	<0.001	1.10 (-0.40, 2.61)	0.279
Day0-Day30	15.44 (8.72, 22.15)	<0.001	2.12 (-0.78, 5.02)	0.285
Day10-Day20	4.46 (1.39, 7.52)	0.002	0.50 (-0.90, 1.90)	1.000
Day10-Day30	8.05 (3.90, 12.19)	<0.001	1.52 (-1.35, 4.38)	0.862
Day20-Day30	3.59 (1.56, 5.62)	<0.001	1.02 (-0.64, 2.67)	0.553

*Pair-wise comparisons using paired-t test with Bonferroni correction; P<0.05 is significant.

Table III: Predicting robust wound healing by univariate and multivariate logistic regression Analysis

Variable	Univariate Logistic Regression			Multivariate Logistic Regression		
	Unadjusted b	Crude OR (95%CI)	p	Adjusted b	Adjusted OR (95%CI)	p
Group						
Control		1.00	<0.001		1.00	<0.001
HBOT	2.91	18.4 (4.93, 68.70)		3.78	43.96 (7.18, 268.97)	
Wound Size at Baseline (cm2)	-0.01	0.99 (0.97, 1.01)	0.309	-0.03	0.97(0.94, 0.99)	0.040
DFU Duration (week)	-0.44	0.96 (0.88, 1.04)	0.301	-0.06	0.94(0.86, 1.03)	0.167

*Forward LR Multivariate Logistic Regression model was applied.
*Multicollinearity and interaction term were checked and not found.
*Hosmer-Lemeshow test yields a p-value of 0.547. The classification table (overall correctly classified percentage at 84.5%) and the area under the ROC curve (96%) were applied to check the model fitness.

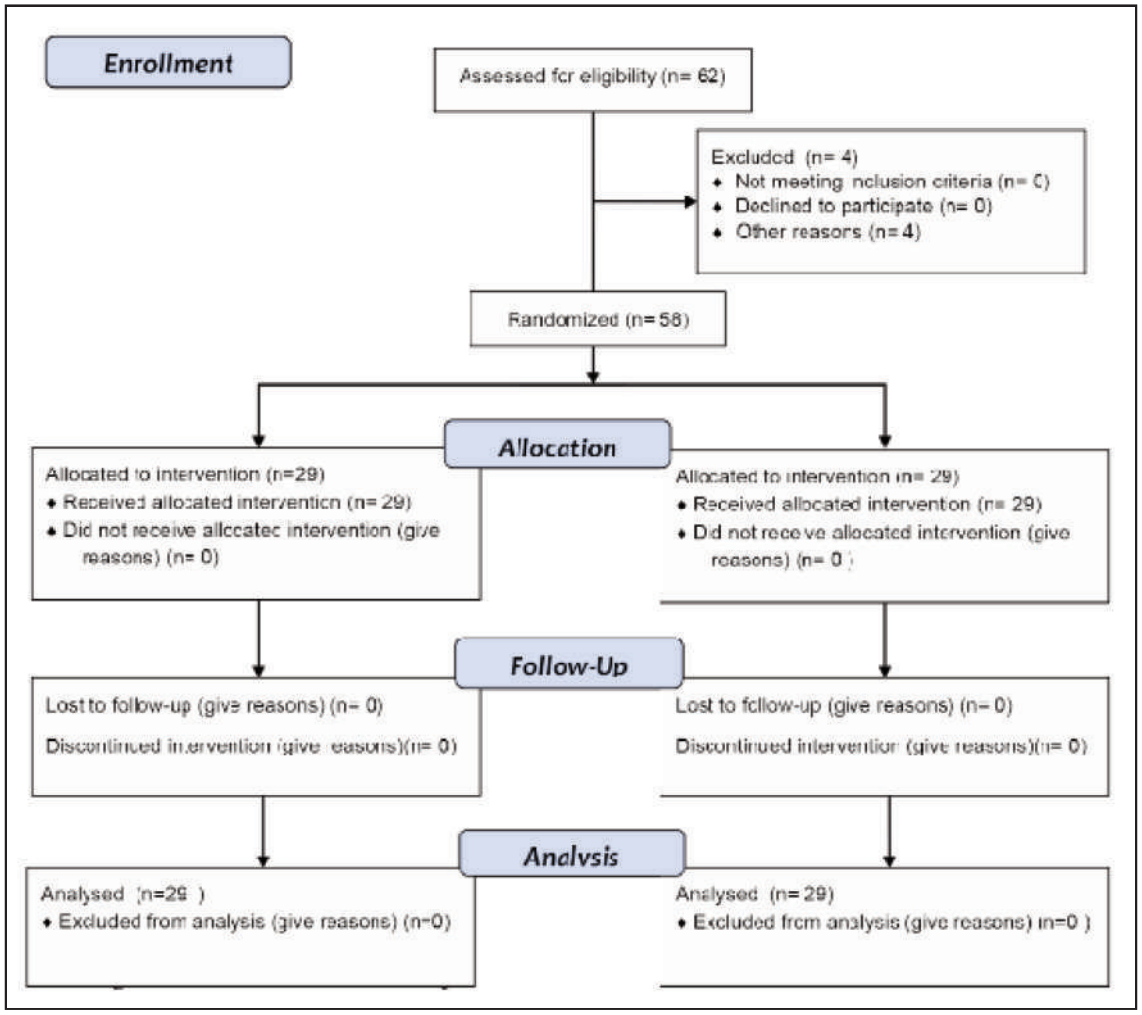

Fig. 1: CONSORT 2010 Flow Diagram

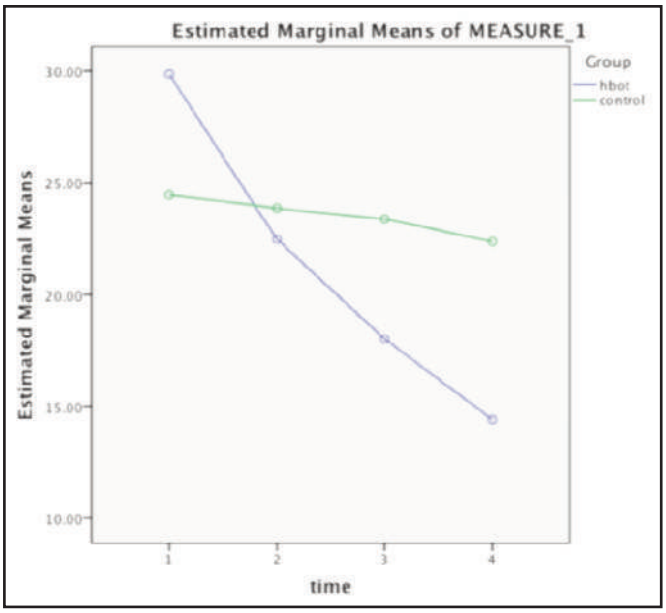

Fig. 2: Profile plots of comparison of means (cm2) of both HBOT and control groups at each time-point (Day 0, 10, 20, 30)..

During the period of this study a few limitations were encountered. There were some challenges that investigators needed to overcome in completing the study. The cost of conducting this clinical trial was expensive and funding was stretched to cover the number of subjects needed from the sample size calculation. Due to this reason we were not able to replace the candidates who dropped out from the study. Unfortunately, no cost effectiveness of HBOT on DFU treatment was analysed because it was not part of study objectives. From transcutaneous oximetry procedures to transportation allowances, the research fund was carefully allocated to ensure completion of the research phases based on the number of subjects intended for this research. One of the biggest challenge in this study was the coordination of study protocol among the collaborating centres. As patients were being referred from specialist clinics from different hospitals, details of patients' medical information and their medical records were confidential and therefore, full cooperation from co-investigators and medical officers were intensely monitored by the principal investigator. In addition to that, since patients were referred from different hospitals under the care of different co-investigators, it was utmost crucial to ensure that all patients, regardless of group assigned received the same standard of conventional wound

care that included standardised data collection involving wound measurement and photograph taking procedures. Attendance compliance was also an issue for patients in both HBOT and control groups. As we depended on time to record the wound healing progress, it was important for the participants to adhere to the schedules given. Another challenge we faced was the possibility of drop out during the treatment program as well as at evaluation period. This tend to happen as soon as or close to the time of wound healing. However, the investigators managed to ensure the selected samples of patients completed a minimum of thirty sessions of HBOT as well as obtained records of wound size and photos.

This study has proven that HBOT has an imminent potential both for clinical and research use among the chronic DFU patients. The future plan is to convince the primary treating physician such as orthopaedic surgeons and internal physicians to include HBOT as part of a must adjunct therapy modality for difficult healing wound. This research has proven the efficacy of the HBOT in promoting faster wound healing and with careful selection of patients it may reduce lower limb amputation rate.[32] The potential for expanding the research within the same field is immense. HBOT can be applied for other type of chronic and difficult healing wound in which fundamental studies can be applied by using HBOT as treatment modality. A hyperbaric research facility that is placed in a hospital would greatly benefit the execution of the research methodology. This will simplify the logistic issues that includes patient handling and significantly reduce the expenses by subtracting the transport allowance. Calculating cost effectiveness of HBOT on DFU cases will further enlighten the treating physician on economic perspective of this treatment modality which can be carried out in future research project. Short stay of the patient in the hospital would improve the control of patients' diabetic condition, diet and wound management as they would be closely monitored by physicians. We would also recommend the use of a multi-place hyperbaric chamber for future HBOT clinical research as it provides a better monitoring access for the patients undergoing HBOT.[33] This is because not only is the multi-place chamber equipped with hyperbaric-compatible monitoring devices such as TCOM probes, electrocardiogram (ECG) machine, blood pressure monitoring and syringe pump, an inside attendant who is normally a nurse will also be with the patients inside the chamber throughout the treatment. Finally, it is important to note that a multi-place hyperbaric chamber enables a sham treatment that is commonly designed for a double-blinded HBOT clinical research.

CONCLUSION

In general, nearly all wound cases of DFU in the HBOT group responded well to the treatment however, the rate at which the wound healed or achieved closure differs from one another. Although HBOT can be a powerful adjuvant in managing DFU, it is only part of a coordinated approach to solve the problem. In conclusion, the results of this randomised controlled trial has shown that HBOT plays an important role in the enhancement of wound healing for diabetic foot ulcers. Compared to the standard wound management alone, wound healing was found to progress at a faster rate when combined with HBOT as an adjunctive therapy.

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ETHICAL APPROVAL

The study has obtained approval for ethics and human research from the USM ethical committee registration USMKK/PPP/JEPem [223.3 (01)].

DECLARATION

The authors hereby declared that the research work and manuscript preparation were carried out without any conflict of interests.

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