Randomized controlled clinical trial evaluating the efficacy of hyperbaric oxygen therapy in facilitating the healing of chronic foot ulcers in diabetic patients: the study protocol

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Study protocol

Keywords: Diabetes Mellitus; Diabetic Foot; Hyperbaric Oxygenation; Wound Healing

Posted Date: November 5th, 2019

DOI: https://doi.org/10.21203/rs.2.16819/v1

Version of Record: A version of this preprint was published on September 29th, 2020. See the published version at https://doi.org/10.1186/s13063-020-04757-6.

Abstract

Background: Diabetic limb ulcers are highly prevalent and contribute to a significant increase in cost for the treatment of these patients in health services. However, healing of these wounds is a major health problem and may even lead to amputation. The aim of the current study is to evaluate the efficacy of hyperbaric oxygen therapy (HBOT) in facilitating the healing of diabetic foot ulcers and reducing the number of amputations in these patients.Methods : The study will be conducted in the city of Imperatriz, Maranhão from 2019 to 2020, in diabetic patients with chronic foot ulcers (classified as Wagner grade 2, 3, and 4, persisting for more than one month). The outpatient follow-up for diabetic foot patients will be done at the SUS (Unified Health System), with a sample size of 120 patients (60 patients for each arm). Half of the patients will receive standard treatment, i.e. dressings, debridement, antibiotics, and load relief, along with HBOT (HBOT group), and the other half will receive only standard treatment (control group). The patients of the HBOT group will be evaluated upon admission, after 10, 20, 30 and 35 HBOT sessions, and after six months. The patients of the control group will also be evaluated at equivalent periods. The progression of the wounds and specific treatment, such as appropriate bandage, antibiotic therapy, or need of some surgical intervention will be evaluated on a weekly basis. The SF-36 quality of life questionnaire will be filled upon admission and after three months of follow-up in both groups. Upon admission, the patients of both groups will undergo arterial Doppler ultrasound, and laboratory tests– complete blood count, erythrocyte sedimentation rate, C-reactive protein, creatinine, fasting blood glucose, and glycosylated haemoglobin.Discussion : Diabetic foot ulcers are a highly prevalent complication of diabetes with serious consequences. A study to assess the efficacy of HBOT in healing the ulcers and reducing the rate of amputations in diabetic patients is justified, which will eventually aid in the development of guidelines for treating these ulcers.

Background

Globally, more than 400 million adults suffer from diabetes, and the treatment of diabetic foot ulcers is considered as an important public health issue [1]. According to the Ministry of Health of Brazil, the number of Brazilians afflicted with diabetes increased by 61.8% between 2006 and 2016, and the prevalence increased from 5.5% to 8.9%, with more prevalence in women (9.9%) than in men (7.8%). Approximately one in every twenty diabetic patients develops foot ulcers in the first year, and approximately 10% of the patients with ulcers evolve to amputation in this period [2, 3].

Unhealed and infected wounds in diabetic foot cause damage in both tissues and bones, which leads to amputations in 85% of these individuals, and 60% mortality has been reported after amputation during five years of follow-up [4-6].

Chronic changes that occur in the feet of diabetic patients, such as peripheral arterial disease, neuropathy with loss of protective sensitivity, deformities, and decreased mobility of the feet, are the main challenges in the prevention and treatment of diabetic foot ulcers [7]. The treatment of diabetes and diabetic foot ulcers requires multiple approaches, which involve optimisation of glycaemic control, wound care,

treatment of infections, load relief and revascularisation in ischemic cases [2, 8]. Unfortunately, even with optimal care, the rate of complete healing of the wounds stays below 60% per year [2, 9]. Hyperbaric oxygen therapy (HBOT) has been used as an adjuvant therapy for patients with refractory ulcers [10, 11].

Normal wound healing occurs through the ordered and overlapping stages of haemostasis, inflammation, proliferation, and tissue remodelling, involving complex molecular and cellular interactions within the wound microenvironment [12]. Regardless of the aetiology of the wound, an adequate condition of the vasculature, including both macrocirculation and microcirculation, is critical for healing. Insufficient perfusion impairs angiogenesis, collagen deposition, and epithelialisation and may lead to sustained inflammation [13].

Among the advanced therapeutic interventions for wounds, HBOT has the unique ability to improve tissue hypoxia, reduce pathological inflammation, and mitigate ischemia-reperfusion injury. The majority of the conditions in which HBOT has been used are known to have a few successful alternative treatments, but the morbidity and mortality associated with the failure of these alternative treatments remains significant [14].

Evidence on the effectiveness of HBOT in healing diabetic foot ulcers is variable. Some researchers have reported greater effectiveness when HBOT is compared to sham treatment or placebo [2, 15-18], but others found no differences [7, 19]. HBOT has also been reported to promote the resolution of infection and reduce the likelihood of amputation by some authors [16], but others have shown no benefit [7, 20].

A systematic review of randomized clinical trial data recently published by the Cochrane Collaboration [21] reported a significant improvement in short-term (6 weeks) wound healing, but no statistically significant difference was found in wound healing rates for long-term amputation and major or minor amputation favouring HBOT, thus, suggesting the need for further randomized studies to clarify these doubts.

Objectives

Primary objective

To assess whether HBOT along with the standard treatment of chronic diabetic foot ulcers is more effective in wound healing than the standard treatment alone.

Secondary objective

To assess whether HBOT, along with the standard treatment of chronic diabetic foot ulcers, reduces the number of major (forefoot, transtibial, or transfemoral) and minor amputations (fingers and transmetatarsal), and improves the quality of life of these patients, as compared to the standard treatment alone.

Hypothesis

Adding adjunctive treatment of HBOT to the standard treatment of diabetic foot ulcers, i.e. dressings, debridement, antibiotics, and load relief, can improve wound healing and reduce major amputations, leading to reduction of costs in some cases and improving the quality of life of these patients.

Methodology

Study Design

This is a parallel, two-arm, non-blinded, randomized controlled trial.

Study site

The study will be conducted in the city of Imperatriz, MA in diabetic patients with chronic foot ulcers (classified as grade 2, 3 and 4 of Wagner [22] and persisting for more than one month). The outpatient follow-up for diabetic foot patients will be done at the SUS (Unified Health System - a public health service for the entire Brazilian population), with HBOT sessions being held in the CicatrizAR Clinic.

Sample and Study Period

The sample will consist of diabetic patients with chronic foot ulcers treated with standard methods, i.e. dressings, debridement, antibiotics, and load relief, along with HBOT (HBOT group), and the other group will be treated only with standard methods (control group), from 2019 to 2020.

The sample size has been calculated based on the formula for comparing two independent groups according to qualitative variables [23], with 95% confidence interval and 80% power. A cure rate of 90% was considered for the case group and the control group had less than 20% cure rate. Thus, the sample size comprised of 60 patients per group

Trial Status

Registration number RBR-7bd3xy. Registered 17 July 2019. The first recruitment was held on 04 July 2019 and the last recruitment is foreseen on 31 August 2020.

Eligibility criteria

The inclusion criteria of the study are adult patients (age > 18 years), stable clinical presentation, diabetes type 1 and 2, Wagner Grade 2, 3, and 4 foot ulcers, ulcers persisting for more than one month without cure, authorisation for the study, and patients of the SUS (Unified Health System).

Exclusion criteria of the study are failure to meet one of the inclusion criteria, patients with macroangiopathy (absent distal pulses), and patients with contraindications for HBOT, absolute or relative, patients on bleomycin chemotherapy, with chronic obstructive pulmonary disease, previous spontaneous pneumothorax, chronic sinusitis, chronic otitis media, unstable angina, severe congestive heart failure, claustrophobia, severe dementia, depression, and history of seizures.

Data collection

The data collection will be performed in the diabetic foot outpatient clinic of the SUS and in the CicatrizAR clinic, using a standardised questionnaire provided in the Supporting Information, as well as with photographic recording of the ulcers, according to the timeline described in Figure 1.

Randomization

This is a parallel, two-arm, non-blinded, randomized controlled trial in which an aleatory randomization will be performed using a simple draw 1:1 by the research coordinator.

Interventions

The patients of the HBOT group will be evaluated upon admission, after 10, 20, 30 and 35 HBOT sessions and after six months; and the control group will also be assessed at equivalent periods to clinically evaluate the ulcers and perform specific measures using the software ImageJ, developed at the National Institutes of Health (NIH, Bethesda, Maryland). The progression of the wounds and specific treatment such as appropriate bandage, antibiotic therapy, or need for some surgical intervention will be evaluated on a weekly basis. The HBOT sessions will be conducted five days a week, being carried out with patients in a multiplace chamber at 2.5 atmospheres absolute (ATA) and 100% O_2, with 10 minutes for compression and decompression, effective sessions of 90 minutes, with intervals of 5 minutes for each 30 minutes of treatment. The dressings will be done in both groups with Exufiber foam Ag ® (*Molnlycke*, Gotemburgo, Suécia) or Mepilex® (*Molnlycke*, Gotemburgo, Suécia), which will be chosen according to the characteristics of wounds, with silver dressings for the infected injuries and a foam with polyurethane protective layer for wounds in which granulation tissue has formed.

The SF-36 quality of life questionnaire will be filled upon admission and after three months of follow-up in both the groups. On admission, the patients of both groups will undergo arterial Doppler ultrasound, and patients with macroangiopathy will be excluded from the research. Laboratory examinations, such as a haemogram, erythrocyte sedimentation rate, levels of C-reactive protein, creatinine, fasting blood glucose, and glycosylated haemoglobin will also be estimated.

Primary outcome

Healing or wound size reduction will be assessed by evaluating the diameter of the lesions by specific software and periods, as described in the interventions.

Secondary outcome

Amputation rates will be assessed, with an evaluation of statistical significance between the groups. The evaluation of the domains of the SF-36 quality of life questionnaire will also be done in both groups. The data from this questionnaire upon admission and after three months of follow-up will be compared.

Data analysis

The collected data will be stored in a Microsoft Excel 2016 spreadsheet format. After checking for errors and inconsistencies, descriptive examinations will be performed by means of absolute and relative frequencies and measures of central tendency and variability.

The chi-square test or an equivalent test will be used to assess associations between the categorical variables and in the case of significant 2×2 associations, odds ratios (ORs), and confidence intervals will be calculated by means of logistic regression. Student's t-test or a similar non-parametric method will be used for the analysis of continuous variables. All examinations will be performed at 5% significance in the IBM SPSS® program, Version 24.0, 2016 (IBM, Armonk, New York, USA).

Ethical aspects

This study will be based on the principles of Resolution 466/12 of the National Health Council that regulates the research involving human subjects. The patients involved shall be duly informed and clarified about the importance and purpose of the study; if patients accept to participate, they will sign an informed consent form. The non-participation in the study or waiver, privacy, reliability, and anonymity of the participants will be guaranteed.

The study was initiated after approval by the Research Ethics Committee of the ABC University. It is registered with the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-7bd3xy.

Adverse events

This study is being conducted in accordance with the guidelines of the Brazilian Society of Hyperbaric Medicine (SBMH), and if adverse events occur, these will be conducted according to these guidelines, as well as be documented and published later.

Discussion

The current study has been designed to compare the existing standard treatment for chronic foot ulcers of diabetic patients, i.e. dressings, debridement, antibiotics, load relief, and their combination with HBOT. Since we do not believe in comparing the two groups with pseudotherapy, it will not be performed on any patient as described by O'Reill et al. and Londahl et al.[7, 24]. Subpressurising or pressurinsing as a placebo would alter the normal physiology of patients' blood gases, which does not occur in standard treatment. Therefore, we believe in the power of evidence that can be provided with this proposed study model.

Abbreviations

HBOT, hyperbaric oxygen therapy

OR, odds ratio

SUS, Unified Health System

Declarations

Ethics approval and consent to participate

This research has been approved by the Research Ethics Committee of the Faculty of Medicine of ABC-SP, under opinion number 3.345.550, provided in the supporting files. Being registered in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-7bd3xy, with the protocol: Does hyperbaric oxygen therapy facilitate healing of chronic foot ulcers in diabetics? It is in accordance with the Helsinki Declaration, with all participants signing the free and informed consent form.

Consent for publication

Not Applicable.

Availability of data and materials

Data and materials will be available as soon as they are collected. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

We, as the authors, declare no conflicts of interest in relation to the study.

Funding

Financial information: There was no funding by any institution.

Authors' contributions

JRAL, MD'AD, and JAC conceptualized the study. JRAL, MD'AD, and JAC designed the methodology. JRAL, MD'AD, JAC, MABB, and LKDG wrote the manuscript. JRAL, MD'AD, JAC, MABB, and LKDG reviewed and edited the manuscript.

Acknowledgments

We thank the hyperbaric doctors of the CicatrizAR clinic, who will assist in the execution of this study.

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Supporting Information

Research Questionnaire

Opinion of the Research Ethics Committee

Informed Consent Form

Figures

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocatin					Close-out
TIMEPOINT		0	*2 weeks*	*4 weeks*	*6 weeks*	*7 weeks*	*3 months*	*6 months*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Vascular exam	X							
History and Demographics	X							
Wound classification (Wagner)	X							
Wound measurements	X		X	X	X	X	X	X
Digital photograph	X		X	X	X	X	X	X
Laboratories	X							
Doppler Ultrasound	X							
Quality of life (SF-36)	X						X	
Allocation		X						
INTERVENTIONS:								
Control Group			X	X	X	X		
HBOT Group			X	X	X	X		
ASSESSMENTS:								
Baseline variables	X	X						
Outcome of Control and HBOT Groups			X	X	X	X	X	X
Quality of life (SF-36)	X						X	X

Figure 1

Spirit Figure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITFillablechecklist15Aug2013.pdf
- InformedConsentForm.pdf
- ResearchQuestionnaire.pdf