Continuous Diffusion of Oxygen (CDO) Treatment for Healing of Diabetic Foot Ulcers

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The University of Texas Southwestern Medical Center
Institutional Review Board

Title: Continuous Diffusion of Oxygen (CDO) Treatment for Healing of Diabetic Foot Ulcers
Principal Investigator: Lawrence A. Lavery, DPM, MPH
Sponsor: EO_2 Concepts

1. Introduction and Purpose

The purpose of this project is to treat diabetic foot ulcers using a continuous diffusion of oxygen therapy (CDO), which will be administered using a portable device. Changes in cutaneous circulation, growth factors, and inflammatory cytokines will be evaluated before, during and after treatment with CDO.

Specific Aims and Outcomes

Aim 1. To evaluate changes in cutaneous circulation before, during and after treatment with topical oxygen device.

H1: Wounds treated with CDO will have better cutaneous circulation and tissue perfusion than wounds treated with standard of care.

H2: Better tissue perfusion will result in faster wound healing

Primary Endpoint

- Comparison of measurements in vascular perfusion, which will be conducted with the following analyses
    - Hyper spectral imaging (Hyper Med)
    - Transcutaneous oxygen measurements

Aim 2. To evaluate changes in growth factors and inflammatory cytokines before, during and after treatment with oxygen device.

H1: CDO treatment will improve levels of growth factors and cytokines involved in the wound healing process as compared to wounds treated with standard of care

Primary Endpoint

- Comparison of measurements in gene expression
    - Inflammatory cytokines: IL-6, IL-8, TNF-α
    - Growth Factors: VEGF, PDGF, IGF, TGF-β

Aim 3. To evaluate changes in bacterial infection before, during and after treatment with oxygen device.

H1: CDO treatment will improve bacterial infection as compared to wounds treated with standard of care

Primary Endpoint

- Comparison of quantitative measurements in bacteria
- Comparison of qualitative analysis in bacteria

2. Background

Diabetes and DFUs Diabetes is a growing global epidemic. In 2010, 6% of all adults, or approximately 285 million people globally, were affected by diabetes. This number is expected to rise by 1.7% in the next 20 years, affecting 439 million adults worldwide. [1] The growth of diabetes appears worse when considering United States alone, where the number of people diagnosed with diabetes increased by 26% from 2007 to 2012. [2] It is anticipated that by 2050 1 in 3 adults in the United States will be diagnosed with diabetes. [3] While the disease affects many adults, the financial burden is extremely high. In 2012, the national cost associated with diabetes reached $245 billion, where 72% directly relates to health care expenditures. [2]

Diabetic patients are prone to end-organ damage due to extensive hyperglycemia. The most common complication is development of foot ulcerations. Approximately 25% of all diabetic patients will develop a foot ulcer over their lifetime. [4] Characteristics of a diabetic foot ulcer include: peripheral neuropathy, inflammatory cytokines, susceptibility to infection, and vascular disease or poor arterial circulation. [5] Patients with a diabetic foot ulcer (DFU) are at high risk for lower-extremity amputation. [6] DFUs account for more hospital admissions compared to any other complication of the disease, and amputation is 15 times more prevalent in a patient with a DFU than in non-diabetic patients. [7] DFUs preceded approximately 100,000 non-traumatic lower-limb amputations in 2008. [8] After an amputation, the mortality rate ranges from 35-65% at 3 years following the procedure. [4]

Oxygen in wound healing Oxygen (O_2) plays an important role in nearly every step of the wound healing process. [9] O_2 is crucial for collagen synthesis, cell proliferation, antimicrobial activities, tissue repair, differentiation of fibroblasts, and angiogenesis. [10-12] In the wound environment, O_2 will form reactive oxygen species (ROS), such as H_2O_2. O_2 exposure has been shown to upregulate vascular endothelial growth factor (VEGF), and ROS will act as a signaling molecule for other cytokines and growth factors such as transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), platelet derived growth factor (PDGF), insulin like growth factor-β (IgF-1β) and interleukin-8 (IL-8). [12] Specifically, O_2-derived H_2O_2 is known to signal PDGF, regulating cell growth and division [13-17].

Delivery of oxygen to a wound depends on several factors, including blood hemoglobin level, capillary density in the wound and its periphery, local oxygen consumption, and peripheral perfusion rate. [9, 11] Ischemia, characterized by hypoxia and nutrient deficiencies, can occur in DFUs, when there is a lack of perfusion in the wound area. [18] Hypoxia is a condition where oxygen delivery is reduced. Wound tissue hypoxia is known to impair wound healing and may occur when local O_2 demand has increased, pathological changes in the vascular bed, periwound fibrosis, and local reduction of tissue perfusion. [9, 18]

Clinical Use of Topical Oxygen Treatment Healing a DFU or surgical foot wound requires optimal tissue perfusion in the wound. [19] One way to increase tissue perfusion is through application of O_2. There are two clinically tested methods for delivery of oxygen to a wound. Hyperbaric Oxygen (HBO) provides pure oxygen systemically at elevated pressures. However, some patients can suffer from oxygen toxicity by an increase in free radicals in the blood, which causes damage. [20]

The danger of O_2 toxicity can be mitigated by directly treating the wound itself, which is done with topical oxygen therapy (TOT). The TOT technologies do not involve high pressure, are not a form of systemic treatment and do not pose risk of oxygen toxicity.

Clinically, TOT has been shown to provide better wound closure and angiogenesis compared to HBO in chronic wounds. [14] In a 14-week, non-randomized prospective study by Gordillo et al., TOT significantly reduced the size of the treated wound ($p < 0.0001$) compared to HBO. TOT also showed a significant increase in VEGF expression ($p = 0.031$) in the wound compared to HBO. VEGF is the most well-known growth factor to stimulate angiogenesis.

Another study was conducted by Tawfick and Sultan, where TOT was evaluated against conventional compression dressings (CCD) over a 12 week period. [21] In this parallel group observational comparative study, 89% of the TOT wounds showed reduced wound area after 3 weeks of treatment compared to 68% of the CCD treated wounds. 80% of the TOT wounds were completely healed at the end of the 12 week period compared to 35% of the CCD treated wounds ($p < 0.0001$). The mean reduction of wound area at the end of the study was lower for the TOT wounds at 96% compared to 61% for the CCD treated wounds.

Innovation

Although the TOT treatment has demonstrated improved wound healing over both HBO and conventional dressings, there are still major disadvantages. Treatment is generally offered for short periods of time, (5 days a week). While undergoing treatment, patient mobility is restricted. Patients must visit the hospital to receive treatments, increasing travel and clinic costs. O_2 also cannot be stored in wound tissues. Once each TOT or HBO treatment is completed, O_2 levels in the wound cannot be maintained. The challenge in topical oxygen therapy is to develop a treatment where oxygen levels can be maintained and provide a continuous supply of O_2 to the wound.

This study will utilize a new innovation in topical oxygen treatment technology called Continuous Diffusion of Oxygen (CDO). The TransCu O_2® handheld device is lightweight, silent, and rechargeable. The TransCu O_2 provides continuous O_2 exposure to the wound. The TransCu O_2 produces oxygen, and is connected to a Moist Wound Therapy dressing, where a moist wound environment and constant flow of O_2 is maintained in the wound. Patients will remain mobile using the TransCu O_2 device, and be provided an at-home therapy for constant use between hospital check-ups. The TransCu O_2 comes with a flow rate and pressure monitor to ensure constant O_2 exposure to the wound.

3. Concise Summary of Project

This is a pilot study. Maximum 30 subjects with a diabetic foot ulcer (DFU) or surgical foot wound will be consented in order to have 20 eligible subjects who will be enrolled and completed the study. Study duration will be three weeks. Patients will be consented and undergo debridement as standard of care at day 0. Ankle-Brachial Index (ABI), Monofilament Sensory Test and Vibration Perception Threshold(VPT) test will be performed only at day 0. Tissue samples will be taken at this visit during standard of care wound debridement and these tissue samples of the wound would normally be removed as part of routine debridement. These tissue samples of the wound will be used for gene expression and bacterial analysis(research). The patient will then receive topical oxygen therapy using the TransCu O2 device (research) with moist wound dressings for 21 days. Moist wound

dressings are used as standard of care. Treatment will be initiated during Screening/Baseline visit(day 0) after routine wound debridement, and patient will receive instructions for home use of the device. The patient will be seen for routine wound debridement at days 7, 14, and 21 with a study window of 5 days., Digital photos of the wound, and vascular evaluations (Transcutaneous oxygen measurements and Hyperspectral imaging. will be performed at each study visit(research). Tissue samples will be taken during standard of care wound debridement at every study visit. Results of the data analysis from this project will be used to inform the design of a larger randomized clinical trial.

4. Study Procedures

Schedule of Events				
	Visit/Day			
	Screening/ Baseline- Day 0	**Day 7(± 5 days window)**	**Day 14(± 5 days window**	**Day 21(± 5 days window**
Informed Consent, HIPAA authorization, Inclusion/Exclusion	X			
Demographics and Medical/Surgical History	X			
ABI	X			
Monofilament Sensory Test	X			
VPT Test	X			
Vascular Evaluation (Transcutaneous oxygen(TcPO2) measurements , Hyperspectral imaging)	X	X	X	X
Wound assessment (wound measurements, digital photos)	X	X	X	X
Tissue Samples	X	X	X	X

Ankle-Brachial Index (ABI) is a measurement of the blood pressure in the lower leg compared to the blood pressure in the arm.

Vibration Perception Threshold (VPT) test is a measurement that uses vibration to test how well subject's feet can detect gentle pressure.

Monofilament Sensory Test is a test to assess subject's sensitivity to touch.

Transcutaneous oxygen (TcPO2) measurements is a test to measure the amount of oxygen in blood.

5. Sub-Study Procedures

6. Criteria for Inclusion of Subjects

- Male or female subjects of all races and ethnicities, age 18-89
- Diagnosis of diabetes mellitus
- Has a diabetic foot ulcer
- Has a surgical foot wound

7. Criteria for Exclusion of Subjects

- End-stage renal disease (ESRD)
- HIV, hepatitis, autoimmune disease, Systemic lupus erythematous (SLE), Raynaud's disease
- Ankle-Brachial Index (ABI) < 0.4
- Unable or unwilling to provide informed consent

8. Sources of Research Material

Sources of research material will include: electronic medical record, demographics (age, gender, ethnic origin), vascular evaluation, wound assessment, digital photos, examinations of the wound, results of the analysis of tissue samples, bacteria culture, adverse events and treatment.

9. Recruitment Methods and Consenting Process

Potential subjects will be identified from Dr. Lavery's inpatient and outpatient populations. This is a treatment study, so subjects participating in other protocols will not be eligible to participate.

When a potential research subject is identified, the Lead Coordinator (or another designated member of the research team) will introduce himself/herself to the potential subject and provide a brief description of the research protocol. S/he will emphasize that participation in research is voluntary and ask the potential subject if he/she would be interested in learning more about the study.
If the potential subject expresses interest, copies of the IRB-approved Consent and HIPAA Authorization will be printed from the IRB website in either English or Spanish (subject preference).

The subject can take the Consent and HIPAA Authorization home with them to read and discuss with friends and family prior to conducting the Consent process. They can write down any questions or concerns, and these will be addressed when the subject returns to the clinic.

The Lead Coordinator will contact the subject to determine if s/he is interested in participation, and schedule the Screening/Baseline visit. At the Baseline visit, informed Consent will be obtained prior to the conduct of any study procedures. All study visits and activities will be conducted in the private treatment rooms at The UTSW Wound Clinic and Parkland Wound Clinic.

10. Potential Risks

Risks for Tissue Sampling
The risks for tissue sampling during the debridement of the wound do not increase the normal risks of this standard procedure. These may include discomfort, bleeding or infection.

Risks for TransCu O_2®
No adverse or toxic effects have been reported from the topical application of oxygen.

Hyperspectral Imaging
Because the camera does not touch the subject, there are no immediate risks from use of the camera. The images recorded are a series of bright colors and does not look like a regular image. It is not possible to identify a person based on the images. The images will be kept in a secure office with limited access. They electronic files will be coded with a subject ID number and will not contain any personal information. The electronic files will be kept until the study is completed.
Loss of Confidentiality
Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

11. Subject Safety and Data Monitoring

For this protocol, there will be no formal data and safety monitoring. The principal investigator will monitor:

- Study accrual rate
- Experience of study participants
- Study attrition including participant withdrawals/dropouts
- Patterns of AE's and/or unanticipated events
- Patterns of protocol deviations and/or violations
- Changes in risk/benefit

12. Procedures to Maintain Confidentiality

At consent, the subject will be assigned a subject number which contains no identifying information. All research tissue specimens, source documents and CRF data entry will only have the subject number.

All patient information will be kept de-identified by subject number. Only authorized persons will have access to patient's medical records to collect data. Other researchers may have access to the samples but only with the permission of the PI. The link between the subject name and study ID number will be kept in separate password protected files. Documents containing identifying information will be kept in locked files in the research staffs' locked offices. Per University Policy "ISR-152 Laptop and Desktop Computer Encryption," all electronic study data will be stored on encrypted computers that are password protected.

13. Potential Benefits

Patients receiving the CDO treatment may result in faster wound healing. It is possible patients will receive no healing benefits.

The information gained in this study may benefit others in the future with non-healing chronic wounds.

References:

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The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Texas Scottish Rite Hospital for Children
Retina Foundation of the Southwest
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	Continuous Diffusion of Oxygen (CDO) Treatment for Healing of Diabetic Foot Ulcers
Funding Agency/Sponsor:	EO2 Concepts
Principal Investigator:	Lawrence Lavery, DPM, MPH
Study Doctors:	Lawrence Lavery, DPM, MPH Javier La Fontaine, DPM Peter Crisologo, DPM David Truong, DPM, MS, AACFAS Matthew Johnson, DPM

You may call the Principal Investigator, Dr. Lavery, during regular office hours at 214-648-9159. At other times, you may call him at 214-786-5401.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
The purpose of this project is to treat diabetic foot ulcers (DFUs) or surgical foot wound using continuous diffusion of oxygen (CDO) (topical oxygen) therapy, which will be administered using a portable device. Changes in wound healing will be evaluated before, during and after treatment with CDO.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have a DFU or surgical foot wound.

How many people will take part in this study?
We plan to consent about 30 people in order to have 20 people who will complete this study at UT Southwestern and Parkland Health and Hospital System.

What is involved in the study?
If you agree to be in this study, you will be asked to sign this consent form and will have the following tests and procedures.

Procedures and Evaluations during the Research:

- You will be asked to read and sign this Consent and another document called a HIPAA Authorization. This will allow us to collect, use and analyze information and tissue samples for this research.
- The researchers will collect your name, demographics (age, gender, ethnic origin), vascular evaluation, wound assessment, digital photos, examinations of the wound, results of the analysis of tissue samples, bacteria culture, adverse events and treatment.
- At the time of your procedure, we will obtain a small sample of the tissues debrided from your wound that would normally be considered 'waste' tissue. With the tissue sample, we will have information about the size of the wound, the location of wound, duration of the wound, and the type of sample collected. No personal identifying information will be kept with your sample.
  After the procedure, researchers may go back into medical records to obtain any available information regarding healing progression of the wound, vascular measurements (checking pulses and blood pressure) and neuropathic measurements (evaluating nerve function by checking the ability to feel touch and vibration).

The tests done on your tissue samples in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at your tissue samples to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the tests done on your tissue samples in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Ankle-Brachial Index (ABI) is a measurement of the blood pressure in the lower leg compared to the blood pressure in the arm.

Vibration Perception Threshold (VPT) test is a measurement that uses vibration to test how well your feet can detect gentle pressure.

Monofilament Sensory Test is a test to assess your sensitivity to touch.

Transcutaneous oxygen (TcPO2) measurements is a test to measure the amount of oxygen in your blood.

Hyperspectral imaging is a type of biomedical imaging used to examine the wound. The camera used does not touch you, and there are no immediate risks from use of the camera. The images recorded are a series of bright colors and does not look like a regular image. It is not possible to identify a person based on the images.

In addition to Hyperspectral imaging, digital photos will be taken of the wound using a standard point and shoot camera.

Procedures for storing of samples

The tissue samples obtained for this research will be stored at UT Southwestern Department of Plastic Surgery Laboratories and may be analyzed in the future using additional technologies without you being asked to sign another consent form. Samples will be labeled with a subject number and no identifying information. Access will be limited to Dr. Lavery and those members of his research team he deems necessary to have access. The samples will be stored until the end of the study, when they will be shipped for analysis. No genetic testing (DNA testing) will be done on your samples.

How long can I expect to be in this study?

Your participation in this study will consist of 4 visits over duration of three weeks. You will be consented and receive topical oxygen therapy for 21 days (± 5 days); treatment will be initiated on Day 0 and you will receive instructions for home use of the device. Tissue samples of the wound will be taken for gene expression (the way that your body reacts) and bacterial analysis (infection) at each clinic visit - Day 0, Day 7(± 5 days), Day 14(± 5 days) and Day 21(± 5 days).For scheduling purposes, each scheduled visit will have an allowance of plus (+) or minus (-) 5 days from the original scheduled visit(s).

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Risks for Tissue Sampling

The risks for tissue sampling during the debridement of the wound do not increase the normal risks of this standard procedure. These may include discomfort, bleeding or infection.

Risks for TransCu O_2®

No adverse or toxic effects have been reported from the topical application of oxygen.

Hyperspectral Imaging
Because the camera does not touch the subject, there are no immediate risks from use of the camera. The images recorded are a series of bright colors and does notlook like a regular image. It is not possible to identify a person based on the images. The images will be kept in a secure office with limited access. They electronic files will be coded with a subject ID number and will not contain any personal information. The electronic files will be kept until the study is completed.

Loss of Confidentiality
Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

What are the possible benefits of this study?
If you agree to take part in this study, there may or may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with DFUs in the future. Information gained from this research could lead to better prevention and treatment.

Will I be paid if I take part in this research study?
Yes. You will be paid $35.00 at the end of each study visit. If you stop taking part in this study or are withdrawn by the research team, you will receive payment for only the visits you have completed. For example, if you complete 4 study visits you will be paid $140.00.

There are no funds available to pay for transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Your social security number (SSN) will be given to The University of Texas Southwestern Medical Center in order to process your payment as required by law. This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

If you are an employee of UT Southwestern, your payment will be added to your regular paycheck and income tax will be deducted.

UT Southwestern, as a State agency, will not be able to make any payments to you for your participation in this research if the State Comptroller has issued a “hold” on all State payments to you. Such a “hold” could result from your failure to make child support payments or pay student loans, etc. If this happens, UT Southwestern will be able to pay you for your taking part in this research 1) after you have made the outstanding payments and 2) the State Comptroller has issued a release of the hold.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Parkland Hospital (PHHS).

You retain your legal rights during your participation in this research.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Receive standard care for your diabetic foot ulcer which may include wound dressings and other standard care procedures.
- Participation in a different research study if there is one available for your condition.

Please talk to the researchers or your personal doctor about these options.

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.
Your doctor is a research investigator in this study. He is interested in both your medical care and the conduct of this research study. At any time, you may discuss your

care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

Will my information be kept confidential?

Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- EO2 Concepts
- Research and Testing Laboratory, Lubbock, TX.
- Representatives of government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people, and
- The UT Southwestern Institutional Review Board

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Is there anything else I should know before I decide?

Dr. Lawrence Lavery has financial interest in the company that manufactures the hyperspectral imaging device being used for this study. You should feel free to ask questions about this.

Whom do I call if I have questions or problems?

For questions about the study, contact Dr. Lawrence Lavery at 214-648-9159 during regular business hours and 214-786-5401 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

We would like to keep your personal information in a database and contact you about participation in future research on diabetic foot ulcers. May we have your permission to save your information and contact you in the future?
Please initial:

Yes _____ **No _____**

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
  You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. The information included in your medical record will be available to your health care providers and other authorized persons including your insurance company.

_____

Participant's Name (printed)

_____ _____

Participant's Signature Date Time AM/PM

_____

Name of person obtaining consent (printed)

_____ _____

Signature of person obtaining consent Date Time AM/PM