Effects of Topical Oxygen on Diabetic Wounds

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PROTOCOL

Background:

Diabetes Mellitus is a major public health problem worldwide in the United States. Chronic wounds are a debilitating condition associated with Diabetes. An estimated excess of US$25 billion is spent annually on treatment of chronic wounds and the burden is rapidly growing due to increasing health care costs, an aging population and a sharp rise in the incidence of diabetes and obesity worldwide.

The clinical use of oxygen to promote wound healing began in the 1960s with the administration of systemic hyperbaric oxygen (HBO) to treat wounds. Today, HBO therapy is approved by the Center for Medicare and Medicaid Services (CMS) in the US to treat specific ulcerations. Although HBO is a clearly promising mode of wound therapy, it requires extensive facilities that may not be available to all patients. Moreover, many wound patients cannot tolerate the systemic HBO therapy side effects.

The approach to topically oxygenate wounds using a variety of approaches is distinct from the conventional HBO therapy in numerous ways. For example, topical approaches do not involve high pressure, are not systemic in nature and, therefore, do not pose the uncommon risk of systemic oxygen toxicity. Our researchers among others have extensively demonstrated that wounds may benefit when oxygenated topically and is supported by the published work. [5] Topical Oxygen therapy, defined as oxygen applied topically to a local area, was first used for treatment of pressure sores and skin ulcers three decades ago. By creating an environment of hyperoxia only in the target region it was hypothesized that systemic complications could be minimized while achieving the desirable local wound effects. Oxygen at a pressure of 1.03 to 1.04 atmospheres absolute was allowed to flow over open wounds enclosed by specially constructed boot-like devices for the lower extremity and contoured cup units for sacral lesions. [1,6] Heng et al reported increased healing rates and increased granulation tissue formation in leg ulcers of patients from a controlled study of 6 men receiving hydrogen peroxide wet-to-dry dressings plus Topical Oxygen therapy delivered by disposable polyethylene bags compared to 5 controls receiving hydrogen peroxide wet-to-dry dressings alone. [3, 4] The authors proposed that the mode of action of Topical Oxygen therapy was direct diffusion of oxygen into the open wound bed, wound fluid, surrounding tissue fluid, and proliferating epidermal cells and fibroblasts.

Objective:

To observe the effect of application of topically administered oxygen on risk adjusted

outcomes (healing rates, rate of amputations, post-treatment health complications, cost of care) in 40 diabetic patients with chronic wounds.

This is a pilot study which is intended to collect data to calculate an adequate sample size for a larger registered clinical trial. Eleven subjects were enrolled at The Ohio State University; we intend to enroll 29 more subjects at Indiana University. Due to the small sample size this study will primarily be a feasibility study that will attempt to measure and evaluate differences in the relative theoretical costs of the intervention of topical oxygen therapy on this population and subsequently compare outcomes in areas such as overall health improvements and cost effectiveness.

Primary Outcome: Wound healing rates 16 weeks post treatment as compared to the baseline visit.
Secondary Outcomes: Rate of amputations, post-treatment wound complications such as wound infection, QoL (SF-36)[13], cost of care 16 weeks post treatment as compared to the baseline visit.

For details of outcomes see STUDY ASSESSMENTS AND PROCEDURES

Study design:
The proposed study is pilot/feasibility study, in which the effectiveness of topical oxygen (100%) administered four days per week, for 16 weeks, for the treatment of diabetic foot ulcer (DFU) or chronic wound will be compared with standard of care (SoC) treatment.

- Subjects will be randomized into one of the two patient groups: **Group 1** will only receive standard of care (SoC) treatment.

STANDARD OF CARE THERAPY (SoC):

At the Comprehensive Wound Center, standard of wound care adheres to Clinical Practice Guideline, based on Wound Healing Society recommendations. Standard of care procedures (SoC) are intended to optimize conditions for wound healing and to ensure that a subject's safety is not compromised by taking part in this clinical study. The following standard of care procedures are routinely applied to patients at the Wound Center regardless of the group allocation across the entire duration of his or her participation in the clinical study.

- Wound cleaning and irrigation with normal saline
- Wound Dressings changes (examples below):
  - Non-adhering contact layer: open-mesh primary wound contact layer comprised of cellulose

acetate coated with a soft tack silicone.
    - Non-Adhering gauze dressing: gauze is made of knitted cellulose acetate fabric mesh that is coated with petrolatum emulsion.
- Off-loading:
    - Total contact casts (TCC) represent the best offloading practices.
    - Total contact casts will be changed on a weekly basis, and as needed for large exudative type wounds, twice weekly. An alginate or foam dressing will be incorporated over the foot ulcer prior to application.
    - If the subject is unable to use TCC or has discontinued using TCC for any reason, the subject will be offloaded with a removable cast walker. The reason for not using or discontinuing use of TCC will be recorded.
- If infection is suspected, appropriate therapy should be initiated according to the local therapy guidelines.

- **Group 2** will receive standard of care treatment plus Topical Oxygen Therapy. The provider will continue routine Standard of Care (SOC) that began prior to Topical Oxygen (TO) Therapy. Any changes in SOC will be based upon clinical practice guidelines and at the providers' discretion. [SOC changes will be documented by the research team to be considered during data analysis.]

    - The therapy will be applied in an identical manner utilizing the Topical Oxygen (TO) delivery device (FDA class II device) manufactured by GWR Medical Inc., and will be connected to an oxygen generator/concentrator. The devices maintain a constant pressure of 1.03 ATM which is just slightly above atmospheric pressure and much less than the typical 2.5 ATM used in hyperbaric oxygen (HBO) chambers.
    - All TO treatments will be provided in a home care or extended care (i.e. nursing home) setting.
    - They will be inflated with 100% FIO_2 in the TO group.

Five study visits are planned as a part of this study (Table -1).

Table-1: Study Timeline

Week(s)	0 (Visit 1)	1-3	4 (Visit 2) (+/-2 weeks)	5-7	8 (Visit 3) (+/-2 weeks)	9-11	12 (Visit 4) (+/-2 weeks)	13-15	16 (Visit 5) (+/-2 weeks)
Study Visit	✓		✓		✓		✓		✓
Digital Imaging	✓		✓		✓		✓		✓
Topical oxygen or SoC treatment administered at home	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study Population: 40 chronic wound patients with diabetes will be recruited based on study inclusion and exclusion criteria by the research personnel. Patients will be randomized into one of the 2 patient groups: the topical oxygen group and the other half randomized into the comparison group.

A proportionate stratified random permuted block design will be used to generate random assignments to the two groups. The stratification will be based on the proportion of patients expected to be seen at a wound center with Wagner grade 1, 2, or 3. This method will ensure balance across the groups and strata and will also account for the difference in the severity over the course of the study period. The biostatistician at the Center for Outcomes Research in Surgery will prepare the master randomization assignment list. The clinical research coordinator will administer randomization using REDCap.

Blinding. This is an open label trial. To reduce bias, the personnel involved in evaluating study outcomes will be blinded to treatment group. The standard of care will be provided by their providers at CWC as part of their routine wound care and will not be blinded to treatment group.

Inclusion Criteria:

1) Age ≥18 years
2) Able to give informed consent, willing and able to complete study requirements.
3) Diabetic
4) Chronic wound **OR** Foot Ulcer:
   a. Ulcer present by history ≥ 4 weeks at time of enrollment

b. Compliant with standard wound care regimen

c. If foot wound, Wagner grade 1 or 2, **–OR-** Wagner grade 3

d. Ulcer size : 0.6 cm^2 to 20 cm^2 and has not decreased in size by more than 30% in previous 2 weeks of the enrollment visit

5) Adequate circulatory status, as evidenced by any of the following (for target wound located below the knee):
   - **a.** Ankle Brachial Index (ABI) $\geq$0.7 - $\leq$ 1.20
   - **b.** If ABI non-compressible (ABI >1.2), then toe brachial Index (TBI)>0.5
   - **c.** SPP > 30mmHg
   - **d.** TcOM > 30mmHg
6) At least 4 weeks since revascularization procedure, if one has been performed
7) Able to complete Topical Oxygen Therapy 4 days/week for 16 weeks (must be able to remove existing wound dressing and apply TO2 Boot/ treatment, and then re-dress wound)

Exclusion Criteria:

1) Ulcer in area of radiation treatment.
2) Active malignancy at site of ulcer
3) Current treatment with wound VAC or weekly compression dressings
4) Untreated infection at site of ulcer (i.e. cellulitis or osteomyelitis)
   a. If acute osteomyelitis has been diagnosed, patient may be enrolled only after the infection has been controlled. Including:
      1. Debridement of infected bone if necessary
      2. Patient has received at least 2 weeks of appropriate antibiotics
5) ABI < 0.7 or > 1.2

Study Procedure:

Note: As much as possible, study visits will be completed at the Indiana University Health Comprehensive Wound Center (CWC). However, due to the patient population, visits at the CWC are not always possible. For those who are unable to obtain transportation for research visits, approved research personnel will conduct these visits at the subject's home; the need for home visits will be assessed on a case-by-case basis. Study visits completed at the subject's home will include all of the same visit activities; subjects will be instructed that research personnel cannot perform any other health care services at these visits.

a. Initial Visit (Visit 1):

1. The research staff will screen the patients' medical chart for inclusion and exclusion criteria (current CWC patients only).
2. The informed consent will be presented to the patient.
   - Confirmation of the study eligibility including the inclusion and exclusion criteria will be reviewed with the patient; Subjects who self-refer from outside of the IU system will be asked to sign a release of information form so records can be requested &

reviewed for inclusion/ exclusion criteria.

An ankle brachial index will be completed for subjects with below the knee wounds if not already completed per standard of care since wound onset to confirm study eligibility. Those with an ABI < 0.7 or > 1.2 will be excluded and no further study activities will be completed. These subjects will not be enrolled.

3. Included in this initial (baseline) visit will be:
    - Randomization into one of the 2 study groups per Randomization plan
    - Medical history review
    - Concomitant medication review
    - Wound history review (onset, location, etiology, size, infection status, previous treatments)
    - Digital imaging of ulcer input to Wound Matrix ™
        - The digital images will be input into a secure web based wound management program, Wound Matrix ™ (Wound Matrix, Inc., Chadds Ford, PA, USA) that will be used for planimetric analysis of wound size.
    - Patient will be asked to complete the quality of life questionnaire (SF-36)
    - Point-of-care testing Hemoglobin A1c will be obtained for all subjects who have not had one completed as SoC within 90 days prior to this visit

4. Patients will also be provided with teaching regarding diabetes, footwear, and wound care.
5. Patients will be given a diary (see example at the end) to log their treatment

b. 4, 8, 12 Week Visit (+/- 2 weeks): Subjects will be asked to return to the CWC to complete repeat digital imaging of the ulcer. For those who are receiving wound care at the CWC, as much as possible, study visits will be scheduled in conjunction with regularly scheduled wound care appointments. Additionally, for those randomized to the topical oxygen treatment group, all follow-up visits will be calculated from the first day of topical oxygen therapy. The following will be completed during the study visit:

- Digital imaging of the ulcer to measure the response to therapy
- Any wound or health complications will be noted
- Medication review
- Collection of previous diary
- Disbursement of new diary

c. At Home Treatments (4 consecutive days per week, **treatment group only**):

1. A trained, approved study personnel will first attend the subjects' home

or extended care facility to provide the supplies, instruct and give support on how to use the TO device (performed solely for research purposes only)

- The approved personnel will teach the subject how to use the TO device and instruct the subject to complete this treatment 4 consecutive days a week, followed by 3 days of no treatment.
- The treatment will begin with the study personnel during the first home care (on site) visit:
  - The 90 minute therapy includes the removal of the ulcer dressing, the ulcer is cleansed/ moistened and the extremity is inserted into an FDA cleared single use oxygen delivery device (GWR Medical, Inc. Chadds Ford, PA).
  - If necessary, a band around the wound is prepared for fixation of the Topical Oxygen device by shaving the limb circumferentially over approximately a 10cm band (done at initial treatment and as needed subsequently).
  - After the 90 minutes, the single use device will be removed and disposed of.
    - Wounds will be treated with standard care at the physician's discretion and diabetic foot ulcers (DFUs) will be administered with a standardized offloading boot to distribute pressure across the entire surface of the foot, specifically removing pressure from the ulcer site per SoC (a non-antimicrobial boot).

2. Trained study personnel will be assigned for the subject, who will receive at home support for the treatment. The study personnel will make weekly phone calls to the subject to check on progress with TO therapy; personnel may go to the subject's home/ care facility on as as-needed basis if the subject is having difficulty with the treatment.
3. Subjects will be given a data collection log (diary) to document the date, time and that the treatment was completed. This will be checked at each study visit and will be collected at their next follow-up visit for compliance.
4. Treatments will continue until the ulcer has closed, an amputation (above or below knee) has been performed, the ulcer's healing has stalled (defined that the size of the wound is unchanged or increased in size in the past 2 visits) or 16 weeks of therapy has been completed.

d. SoC group only- Patients will receive Standard of Care for their wound per the study physician's discretion. There will be no at home treatments for this study population but they will be asked to return for follow-up visits at 4, 8, 12, and 16 weeks following their baseline visit.

1. Subjects will be given a data collection log (diary) to document information about the SoC including wound dressing intact, offloading boot being used (for DFU's), the date, and the subject's initials. This will be checked at each study visit and will be collected at their next follow-up visit for compliance.
2. SoC will continue until the ulcer has closed, an amputation (above or below knee) has been performed, or the ulcer's healing has stalled (defined that the size of the wound is unchanged or increased in size in the past 2 visits).

All wounds for both groups will be treated with standard care and will be administered with a standardized offloading boot that distributes the pressure across the entire surface of the foot, specifically removing pressure from the ulcer site will be utilized (a non-antimicrobial boot). Offloading boots are standard of care for these wounds and will not be provided by the study.

Week 16 (FSV) (+/- 2 weeks)/ Follow-up:
Once the patient's ulcer has completely healed or the 16 weeks of treatment ends, the patient will return for their final study visit.

- If complete healing is achieved in less than 16 weeks, a follow-up visit will be scheduled at 16 weeks after enrollment.
    - Patients will be instructed to contact the study Physician should the ulcer recur.
    - The initially assigned oxygen treatments will be stopped at this time.

- Digital imaging of the ulcer to measure the response to therapy
- Quality of life questionnaire (SF-36) will be administered to all patients at 16 weeks.
- If the wound has not healed in 16 weeks, the wound is assessed as to its recent response to treatment.
    - Wounds, which have decreased less than 10% in wound surface area during the preceding 4 weeks, are designated as "Quiescent". Quiescent wounds are considered to be non-responders.

STUDY ASSESSMENTS AND PROCEDURES

a. Wound Healing rates. Wound healing rates will be determined from wound area measurement at baseline vs final visit using wound photography and Wound Matrix. Wound Matrix will be used to capture wound image, instantly upload wound images and obtain measurement of wound area data elements at the point of care. Measurement should be performed after debridement if there is one as a part of SoC. Wound matrix is a digital wound measurement

system that utilizes tablet/smartphone camera for taking a digital image of the wound in presence of a standard Ruler for size calibration. The image is automatically tracked and measured. The software tracks the outer perimeters of the wounds using a proprietary algorithm.

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b. Quality of life assessment
SF-36- All patients will be administered the Medical Outcomes Study Short Form (SF-36) at baseline and end of study. The SF-36 is an indicator of the overall health status[13]

c. Wound complications such as wound infection. The following standard scale for wound infection will be used**:**

Infection Level:

- **Level 0 -** Uninfected or no signs of infection
- **Level 1 – Mild** Infection present with presence of any two of the following items:
  - Local swelling or induration
  - Erythema >0.5 to <=2 cm around the ulcer
  - Local tenderness or pain
  - Local warmth
  - Purulent discharge (thick, opaque to white, or sanguineous secretion)
  - Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below).
  - Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
- **Level 2 – Moderate** Local infection (as described above) with presence of erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)
- **Level 3 – Severe** Local infection (as described above) with presence of the signs of SIRS, as manifested by two or more of the following:
  - Temperature >38 or <36C
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg
  - White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms

d. Cost of care. Cost will be calculated including SOC expenses such as patient-of-pocket expenses and expenses billed to the insurance company, as well as theoretical costs associated with topical oxygen therapy. These

costs will be analyzed through the Comprehensive Wound Center Standard of Care billing. Due to the cost analysis portion of the study, this study will be limited to Medicaid/ Medicare and dual eligible recipients only.

Compliance:

The results of wound care are highly dependent upon compliance with specified treatment regimens. To ensure optimum subject compliance, research staff will counsel subjects at each study visit and assist to facilitate the delivery of appropriate care. Subjects will be encouraged to maintain scheduled appointments and comply with appropriate wound care (TO+SoC or SOC). Study subjects will be asked to record their wound care treatment by using a patient diary between visits. These diaries will be collected at each visit and reviewed for compliance. For the purposes of this study, subjects meeting either of the following criteria will be considered to be major protocol violators:

1. Subject fails to receive wound treatment for 8 consecutive sessions for any reason
2. Any subject who misses more than 30% of scheduled treatments in a month

Any subject assigned to Topical Oxygen Therapy and meeting criteria for major protocol violators in any two months will be discontinued for the duration of the study. Any study subject who is determined to be noncompliant with their care per the discretion of the principal investigator can be removed from the study.

Data Safety Monitoring:

Data will be reviewed by the PI and study coordinator on an ongoing basis.

Adverse events:

Chronic wounds represent a visible manifestation of a highly morbid disease state. As such, during the duration of this study, the natural history of these patients includes a significant risk of infection, limb loss, myocardial infarction, and death. Although expected, these events will be reportable to the IRB (if they meet reporting criteria), which will monitor these events for differences between the two groups. Wounds which are highly exudative (produce copious fluid) and may become macerated or new ulcers may form. These adverse events are all results of the disease state. The use of Topical Oxygen does require that the disposable device be affixed to the skin of the leg with a self-adhesive tape. Patients will be specifically monitored for

disturbed skin integrity at the fixation point. If this occurs, local wound care including skin protectants will be provided and future treatments will employ fixation at a different location, either proximal or distal. If the problem recurs or is of significant severity in the opinion of patient or treating physician treatment will be discontinued.

Benefits:

This pilot study will result in determining if TO may be an effective treatment modality for healing of open diabetic wounds.
Timely access to this modality will significantly benefit the Indiana population with diabetes that suffers from chronic wounds, a costly segment of beneficiaries in Indiana's Medicaid/Medicare and dual eligible program. These improved health outcomes may also result in cost savings to Indiana's Medicaid program. Regardless of the results of this study, the findings may provide insights into the care of this patient population, which will allow doctors to better treat patients in the future.

Alternatives:

Patients do not have to participate in this study to receive treatment for their ulcer. All of the treatments provided in this research study are available outside of this study. If they choose not to participate in this study they may seek these treatments from their doctor or the study investigators.

Payment:

Subjects will be compensated up to a total of $125 for their study participation. Each subject will be paid $25 for the completion of each study visit, for a maximum of 5 visits. Study visits that are completed at the subject's home will be compensated at $15 per visit. Subjects will only be compensated for completed visits. Subjects will receive payment through a pre-paid debit card. All currency is in U.S. dollars and is considered taxable income.

Device Description, Approval Status, References, Role of GWR Medical, Inc. in this study:

Upon initial consideration of TO devices after the passage of the Medical Device Amendments in 1979, FDA initially proposed classification of such devices into Class II based on the evidence of safety and effectiveness submitted to the General and Plastic Surgery Device Classification Panel.[7] However, in the interim between the release of the proposed and final device classification regulations, FDA reconsidered the evidence provided and decided to classify TO devices as Class III due to the lack of sufficient evidence demonstrating safety and effectiveness.[8] Then in 2006, FDA issued a proposed rule to reclassify TO devices as Class II, based primarily on the data presented

in three, then recent, studies.[9,10,11,12]The device is an FDA cleared Class II Device, and not an investigational device. This device is currently being used in many clinical care settings. The U.S. Department of Veterans Affairs and New York Medicaid reimburses TO Therapy that is being given as a SOC treatment using this device.

See attached FDA document titled: Federal Register /Vol. 76, No. 79 /Monday, April 25, 2011 /Rules and Regulations.

Role of GWR Medical, Inc. for this study include the following;

- Provide TO devices for free.
- Provide digital imaging software to capture wound images for wound measurements.

- **Data Management:**

  Data will be collected via paper, phone interviews, direct data capture from measurement instrument and stored electronically in REDCap and xls files on Department Server. The storage location will be backed up manually every week. Other data sources include outside lab data, data from INPC will be stored in separate electronic files and merged with the primary data as needed. Quality assurance steps will include: 1) built-in range checks; 2) testing of database by study team prior to moving to production mode. The following quality control methods will be used: single entry with random checks of accuracy; and 2) extraction and cleaning of data that will be used for analysis every 6 months.

Statistical Analysis Plan:

Sample size. Although the main objective of this pilot trial is not to detect the significant difference between the two study groups, rather to provide preliminary data for the design of future trial, with sample size of n=40 (n=20 in each arm) could also provide at least 80% power to detect superiority of the TO+SoC treatment success rate (50%) vs. SoC (10%) based on a one-sided Fisher's Exact test at a significance level of 0.05.

Statistical analysis.

Univariate analysis will be done using frequencies, mean (SD), median (IQR) to describe the patient cohort. Cumulative incidence of wound healing rates 16 weeks post treatment with 95% confidence interval around the risk estimate will be computed for the two groups (SoC and TO+SoC). Bivariate logistic regression will be used to report the odds of wound healing among those with TO+SoC compared to SoC only. Bivariate analysis to compare secondary outcomes between the groups will be done using Chi-square or Fisher's exact tests for categorical variables and t-tests or Mann-Whitney tests for continuous variables (e.g. QoL ratings from SF-36, costs).

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