A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers

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Abstract

Worldwide, diabetic foot ulcers (DFUs) continue to exact a major burden on patients and health care providers. Although hyperbaric oxygen therapy is well-known as an adjunct option, less is known about the efficacy of transdermal continuous oxygen therapy (TCOT). A prospective, randomized, blinded, multicenter, parallel study was conducted from October 2009 to November 2012 to evaluate healing time and the proportion of DFUs healed after 12 weeks of moist wound therapy (MWT) with or without TCOT. Study participants (persons with type 1 or type 2 diabetes and a nonhealing [>1-month but <1-year duration], 1 cm^2 to 10 cm^2 in area, infection-free DFU) were randomized to TCOT or a sham device (control) in addition to receiving MWT. TCOT treatment consisted of continuous administration of 98+% oxygen to the wound site using a 15-day device with dressings changed every 3 to 7 days per care plan or more often when clinically required. Potential participants completed demographic and clinical screening and wound and laboratory evaluations at baseline, and wound evaluations, evaluation of adverse events, debridement, and treatment once weekly until the wound healed or up to 12 weeks. The primary endpoint was defined as complete wound closure by week 12. Wound measurements were made utilizing acetate tracings. Original tracings were collected at approximately 6-week intervals and analyzed upon study closure. Data were collected via paper Case Report Forms and entered into an electronic database after the patient's final visit. Statistical analysis was performed on datasets exported from the electronic database. Wound measurement data were analyzed using chi-squared. Time to complete closure was analyzed using Kaplan-Meier analysis in conjunction with the log-rank test. Of the 130 potential participants, 8 with protocol violations were excluded from analysis. In the intent-to-treat (ITT) population (N = 122, average age 59 years [range 28–85 years]), the majority were male (74%), Caucasian (81%), and had a plantar ulcer (76%). Mean baseline wound area was 2.3 ± 1.7 cm^2 (range 0.4–8.9 cm^2) and 2.0 ± 1.7 cm^2 (range 0.6–8.7 cm^2) in the control and TCOT groups, respectively. HbA1c (%) was 7.9 ± 1.7 in the control and 8.0 ± 1.7 in the treatment group. In the TCOT group, 35 of 65 (54%) wounds healed compared to 31 of 63 (49%) in the control arm (P = .4167). In the per-protocol population (PP) (ie, patients without protocol violations), 34 of 61 wounds (56%) in the TCOT group and 31 of 61 (49%) in the control group healed. In the ≥65 years PP subgroup, 14 of 17 (82%) in the TCOT and 8 of 16 (50%) in the control arm healed (P = .049). Median time to complete closure in the PP group was 63 days for the TCOT and 77 days for the control group (P >.05). No device-related serious adverse events occurred in either group. Wound outcomes of patients in both groups were good, but the TCOT device did not appear to offer added benefit over moist wound healing treatment and offloading to facilitate the healing of small, nonsevere diabetic foot ulcers of relatively healthy patients. The data suggest the device may offer a greater benefit to older patients. Studies including a more diverse and larger sample patient population are warranted.

Keywords: clinical trial, foot ulcer, diabetic, wound healing, oxygen

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Key Points

- The authors conducted a randomized, controlled, double-blind clinical study to compare 12-week treatment outcomes of patients with foot ulcers secondary to diabetes mellitus.
- Patients were randomly assigned to a moist wound therapy (MWT) regimen with transdermal continuous oxygen therapy (TCOT) or MWT with a sham TCOT device (control).
- Of the 122 evaluable patients, approximately 50% healed in both treatment groups, which was not significantly different.
- Among patients >65 years of age, more TCOT (82%) than control group (50%) patients healed, but this difference also was not statistically significant.
- The author concludes wound outcomes using strict standards of care and MWT were good and that additional studies with a more diverse patient population are warranted.

More than 16 million people in the United States have diabetes mellitus. Among Medicare beneficiaries (≥65 years), the prevalence of diabetes was 25.8% in 2011, and the incidence of diabetic foot ulcers (DFUs) in this subpopulation was 8.2% and 7.8% for men and women, respectively.[1,2] The yearly prevalence of lower extremity amputation (LEA) in Medicare beneficiaries with diabetes was 1.8% in 2008.[1,2] The worldwide diabetic population is estimated to be approximately 347 million.[3] Assuming the proportion of LEA to be approximately the same worldwide, the numbers and associated costs are staggering, not to mention the pain, suffering, and morbidity associated with these amputations. A treatment modality that would improve both the rate and percent of healing for DFUs would be a great benefit to these patients.

Lower extremity leg ulcers in the diabetic population are a source of major concern because of the high risk of developing serious limb-threatening complications. Moreover, in these ulcers, bacterial infection is common and wound hypoxia is well documented.[4]

Oxygen's role in wound healing as described in various review articles is well known. It is thought oxygen helps alter the microenvironment of the wound to enable the healing process.[5] Although mild hypoxia may stimulate angiogenesis and wound repair, both *in vivo* and *in vitro* studies[6-9] have shown near-anoxic hypoxia, commonly encountered in chronic wounds, to impair wound healing. Treatments to ameliorate the oxygen deficiency in chronic wounds include systemic hyperbaric oxygen therapy (HBOT) and topical approaches.[8] Overall, although HBOT has the potential to increase local oxygen pressure, it is also expensive and has some uncommon but important adverse effects on patients, such as otic barotrauma, hypoglycemia, and dyspnea.[10,11]

Local oxygen delivery creates a much smaller increase in oxygen pressure; consequently, it is safer. However, information about its effectiveness for wound healing is limited. A study by Lo et al[12] regarding localized oxygen modulation of wounds in mice found improved collagen maturity when wounds were oxygen-treated when compared to baseline measurements. In considering the level of evidence for increased collagen deposition and tensile strength derived from adjunctive topical oxygen therapy (TOT) applied to wounds, Orsted et al[13] rated it Level IIa (evidence obtained from at least 1 well-designed controlled study without randomization). In their prospective controlled, nonrandomized study of TOT of 132 patients with venous leg ulcers (VLUs), Tawfick and Sultan[14] observed complete closure at 12 weeks in 76% of the 67 TOT patients and 46% in the control group treated with high compression (n = 65). Other controlled animal studies and case series[15-17] in humans regarding healing of wounds with TOT also have demonstrated improved wound healing and/or a reduction in bacterial burden.

Transdermal continuous oxygen therapy (TCOT) is the continuous delivery of a very low dose (3 mL/hour) of 98% pure oxygen directly to the wound site to facilitate uninterrupted treatment.[18] Each TCOT device provides continuous oxygen supply for 15 days. This noninvasive therapy is applied to the wound surface and can be initiated in any care setting, allowing the patient to be ambulatory. The TCOT device is a US Food and Drug Administration (FDA)-cleared pre-amendment Class II medical device intended to provide TCOT for the treatment of skin ulcerations due to diabetes, venous stasis, postsurgical infection, gangrenous lesions, pressure ulcers, amputations and infected stumps, skin grafts, burns, and frostbite. Because of the very low flow rate, the wound does not dry out and a moist wound healing environment is maintained with the use of an occlusive dressing.[19] Wound dressings usually are changed every 3 to 7 days per care plan or more often when clinically required, such as in the case of heavy exudate.

A pilot, prospective, randomized controlled trial (RCT) was conducted by Driver et al[20] to evaluate the biological processes of topical oxygen use through the study of biomarkers. In this study, participants with chronic DFUs who randomly received TCOT (blinded for review) as an adjunct to standard care (SC) for 4 weeks (n = 9) were compared to persons who received SC alone (n = 8). No significant differences were noted in the clinical features of the ulcers between the 2 groups ($P > .05$). At week 4, wound size decreased in ~87% in the TCOT group and ~46% in the SC group; percent area reduction in the TCOT treatment group was significantly and clinically successful at 3 and 4 weeks compared to the control group ($P < .05$).

The purpose of this RCT was to evaluate healing time and the proportion of DFUs healed after 12 weeks of SC with TCOT compared to SC without TCOT.

Methods and Procedures

Study design. A prospective, randomized, blinded, multicenter, parallel study was conducted to compare TCOT with moist wound therapy (MWT) to MWT alone (hereafter referred to as the control) in the treatment of chronic DFUs.

Ethics. This was an Investigational Device Exemption (IDE) study under US CFR 812.2(c)(2). (FDA regulation states medical devices with 510[k[clearance, used or investigated in accordance with the approved indications for use, are exempt from IDE requirement.) However, all aspects of the study were conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki (1989), the provisions specified in Title 21 Parts 50, 54, 56, and 812 of the US Code of Federal Regulations, the protocol, and all federal, state, and local laws of pertinent regulatory authorities. The study was approved by Western IRB (July 2009). The study was registered with clinicaltrials.gov (NCT01291160). Enrollment of the first patient started October 2009, and the study was completed in November 2012.

Study sites. The study research team was led by a lead principal investigator (PI). Neogenix LLC (Norwood, MA) sponsored the trial; data were managed by Amarex Clinical Research (Germantown, MD). Strategic Solutions Inc (Cody, WY) managed statistical analysis. A Clinical Events Committee (CEC) monitored the safety aspects of the study and included 4 US and Canadian medical doctors, including the lead PI. Blood tests were performed primarily at clinical labs used by the investigators. Wound tracings and photographs were processed by Jill S. Kawalec, PhD, Research Division Head at Kent State University, College of Podiatric Medicine, which acted as a central wound core lab for all sites.Twenty-two (22) investigators from 22 US, Puerto Rican, and Canadian wound clinics participated in the project.

Study inclusion and exclusion criteria. Inclusion criteria stipulated participants must be either gender; 20 to 90 years of age; have a diagnosis of type 1 or type 2 diabetes mellitus; and have a nonhealing, full-thickness, University of Texas Classification of Diabetic Foot Ulcers Class IA of at least 4 but not >52 weeks' duration measuring 1 cm^2 to 10 cm^2 in area and located at or below the malleoli. Patients with partial amputation up to and including a transmetatarsal amputation and an ankle-brachial index (ABI) ≥ 0.7 on the study limb; transcutaneous partial pressure oxygen >40 mm Hg; a toe pressure 40 mm Hg; or a Doppler waveform consistent with adequate flow in the foot (biphasic or triphasic waveforms) at screening also were included.

Patients were excluded from participating if their wounds had a duration >52 weeks; there was evidence of gangrene or evidence of active Charcot's foot on the study limb; they were scheduled to undergo vascular surgery, angioplasty, or thrombolysis; they had infected target ulcers accompanied by cellulitis, known or suspected osteomyelitis, or other clinical evidence of infection; the index ulcer had exposed tendons, ligaments, muscle, or bone; the ulcers were present between toes; the target limb was infected at screening or baseline; if they had a history of malignancy on the study limb; they had used oral or IV antibiotic/antimicrobial agents or medications used within 2 days (48 hours) of baseline; were taking steroids; had received growth factor therapy (eg, autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix) within 2 weeks of the screening date; were pregnant; the total surface area of the ulcer was >10 cm^2 at the screening visit as measured by a member of the study staff; they were undergoing renal dialysis; they had known immune insufficiency other than diabetes mellitus; the ulcer decreased in area by >30% during the run-in period; they had a history of peripheral vascular repair within the 30 days of baseline; they were currently receiving or had received radiation or chemotherapy within 3 months of randomization; they had known or "patient-reported" alcohol or substance abuse within 3 months before baseline; they were currently enrolled or participated within 30 days of baseline in another investigational device, drug, or biological trial; they were allergic to a broad-spectrum of primary and secondary dressing materials, including occlusive dressings and the adhesives on such dressings; they had a Chopart amputation; and/or they had an active malignancy except nonmelanoma skin cancer.

The participant and/or caregiver had to be willing and able to learn and perform the duties of dressing changes and demonstrate the ability to do so. If the patient had a history of alcohol or substance abuse within 6 months before the baseline period, proof of treatment needed to be provided.

Patients were screened and sent for laboratory assessments after signing the informed consent document. Screening assessment consisted of 1) medical history; 2) inclusion/exclusion criteria matching (see Table 1); 3) vital statistics (height, weight, blood pressure, systolic blood pressure in arm and ankle, respiratory and pulse rates, and body temperature); 4) wound assessment; and 5) SC wound treatment (removal of necrotic or infected tissue, wound cleansing, establishment of adequate blood circulation, maintenance of a moist wound environment, offloading for plantar ulcers, management of wound infection, nutritional support where needed, and blood glucose control).

If a potential participant passed the screening, he/she was scheduled for a baseline visit 1 week after the screening date and sent for laboratory assessments, including glycated hemoglobin (HbA1c), creatinine, and complete blood count panel. The study participant was randomized providing the HbA1c was <12%, creatinine level was <3 mg/dL, and wound area had not decreased >30% since the screening visit. Baseline assessments included diabetes history, smoking habits, allergies, vital signs, wound location, monofilament testing, wound tracing using Visitrak or Dermal Map mylar grid and felt tip pen, wound photograph, measurement of largest length and width and depth of the wound using a disposable ruler, and wound characteristics (wound edge, base color,

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Between 20 and 90 years of age with a diabetic foot ulcer at or below the malleoli	Oral or intravenous antibiotic/antimicrobial agents or medications have been used within 2 days (48 hours) of baseline
Type 1 or type 2 diabetes with HbA1C[a] <12%	Wounds of >52 weeks duration
Creatinine ≤3 mg/dL	On dialysis treatment
Open wound for at least 4 weeks from day 1 on screening visit	Has infected target ulcers accompanied by cellulitis, known or suspected osteomyelitis, or other clinical evidence of infection
Wound size must be ≥1 cm^2 and <10 cm^2 at screening visit	Ulcers present in between toes; index ulcer has exposed tendons, ligaments, muscle, or bone
Treatment provided if patient has had a history of alcohol or substance abuse within 6 months prior to baseline	Has received growth factor therapy (eg, autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix) within 2 weeks of screening date
No active malignancy except nonmelanoma skin cancer	Scheduled to undergo vascular surgery, angioplasty, or thrombolysis
Has had partial amputation up to and including a transmetatarsal amputation	Evidence of gangrene on any part of affected limb Has active Charcot's foot on the study limb On steroids with >7 mg dosage Pregnant

[a]*HbAlc: glycated hemoglobin*

periwound conditions, periwound color, edema, drainage amount and type, percentage of granulation tissue, and pain level). When plantar ulcers were present, the study participant also was instructed to offload and was provided the appropriate product.

Randomization and blinding. Study participants who continued to meet the inclusion criteria were enrolled into the study by the site investigator or coordinator and randomized to 1 of the 2 treatment groups. The randomization was centralized with a 1:1 ratio (active treatment group: control treatment group), and 2 stratification factors were used: 1) wound size at baseline (≥1 cm^2 to ≤5 cm^2 and >5 cm^2 to 10 cm^2) and 2) patient age at baseline (<65 years, ≥65 years). These stratification factors also were used in analyzing the results of the trial. The randomization schedule was prepared by Precision Sciences Inc (Phoenix, AZ). The actual randomization assignment was made via a web-based centralized system (WebView, Zifo Technologies, Lindenhurst, IL).

All study participants, the investigators, and site staff were blinded to the treatment. In addition, the evaluators who processed the tracings and photographs also were blinded. The active treatment group received the TCOT device, and the control group received a sham "device." TCOT treatment consisted of continuous administration of 98+% oxygen to the wound site using a 15-day device changed every 15 days. Sham units were prepared by assembling the "device" without the oxygen-generating fuel cell assembly. This was done by Sparton Corporation (Plaistow, NH) (blinded for review), which received a copy of the 1:1 randomization schedule to enable the company to prepare kits with either working device units or sham units. The sponsor also was blinded to this randomization process. Allocation concealment was successfully achieved because the devices looked the same regardless of assignment (for example, A or B).

At each study visit, a member of the study staff recorded any adverse experiences, obtained laboratory samples, measured the study wound, collected level of pain information using the Wong-Baker FACES Pain Rating Scale, administered the Standard Form-12 version 2 (SF-12v2) quality-of-life questionnaire to assess patient-reported physical and mental health, performed wound care treatment, and assessed the study wound.

Clinical evaluation and procedures. The device was applied after wound assessment (including recording of exudate and dressing type and wound characteristics as described earlier), cleansing, debridement, and any other wound management of the study participant's wound site as follows: using sterile techniques, the cannula was removed from the cannula packet and attached to the Luer Lock located on the side of the device and tightened clockwise to the maximum finger strength. After determining where the device would be most comfortably worn by the study participant, the clinician measured along the path of the cannula to ensure the cannula was long enough to reach from the wound to the device. The tip of the cannula was placed at the center of the cleaned and debrided wound bed and secured to the chosen dressing with Transpore plastic tape (3M, Minneapolis, MN).

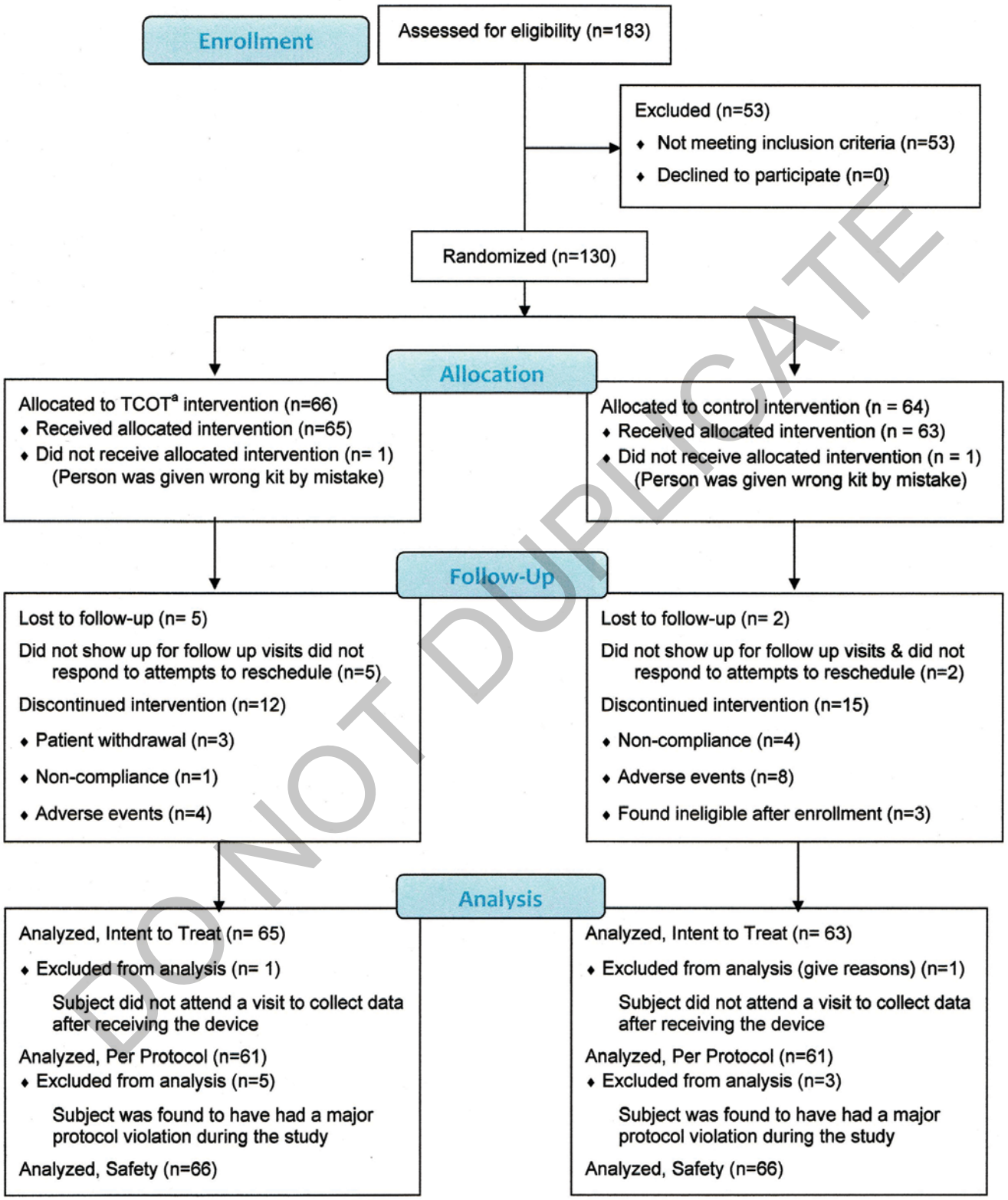

Figure 1. Patient flow diagram. [a]TCOT: transdermal continuous oxygen therapy.

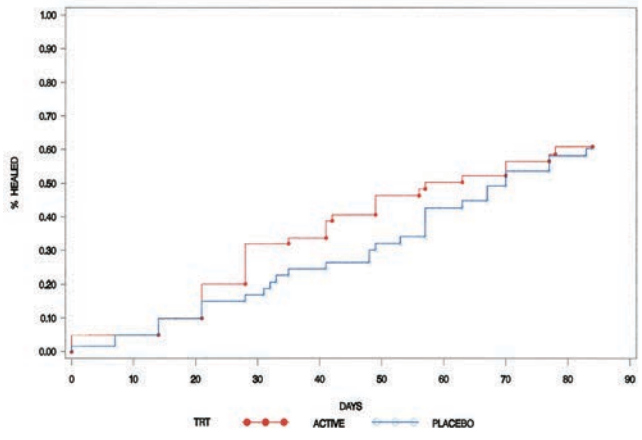

Figure 2. Kaplan-Meier plots for the per-protocol population. (*P* <.05).

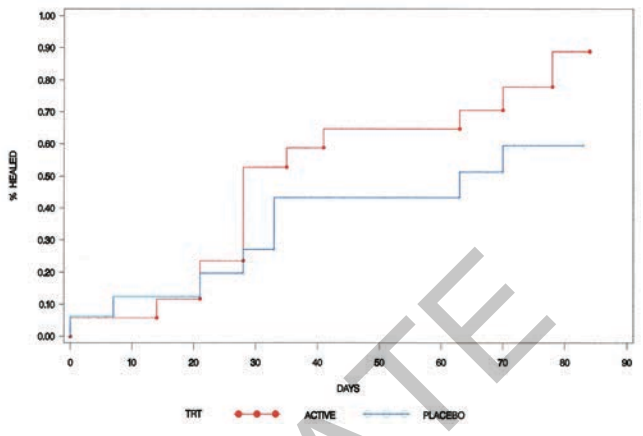

Figure 3. Kaplan-Meier plots for ≥65-year-old patients in the per-protocol population. (*P* <.05).

A dressing selection guide (hydrocolloid or alginate and foam dressing) was included in the protocol to be selected based on the exudate level of the wound. Clinical judgment was used to determine which dressing was best suited for each study participant. To prevent the cannula from embedding into the periwound or wound bed, a padding (gauze or a foam) was placed underneath the cannula on the participant's extremity in the periwound area. The tip of the cannula and the entire wound bed was covered with the chosen dressing and secured with Tegaderm (3M, Minneapolis, MN) transparent film dressing; the film ensured the oxygen would be trapped in the wound bed. A 2-inch margin of film dressing along the edges of the wound was recommended, and the film was pinched around the cannula to reduce any chances of oxygen leakage. The transparent film dressing covered the entire length of the primary dressing. The study participant then was scheduled for a weekly visit for dressing change, change of the spent TCOT device (every other week), and wound assessment. All visits and dressing and device changes were done in outpatient clinics.

When the study participant's wound closed or at the end of 12 weeks of treatment, the treatment was completed and end-of-visit procedures were performed, which included clinical procedures and blood work. If the wound closed on or before the 12-week period, the study participant was scheduled for 2 follow-up visits — the first visit 2 weeks after wound closure and a second follow-up visit 10 weeks after the first follow-up visit, assuming the wound remained closed at the first follow-up visit.

Data collection. Data were collected using Case Report Forms and entered into an electronic database after the patient's final visit. Original acetate tracings were collected throughout the study and shipped to the wound core lab for analysis. Wound measurement analysis was conducted at the end of the study. Statistical analysis was performed using Statistical Analysis System (SAS™, Cary, NC) statistical software on datasets exported from the electronic database.

Statistical analysis. The sample size was generated using nQuery 6.01 (Statistical Solutions, Boston, MA), based on a clinically meaningful difference of 30% in percentage of healed study participants (28.2% of study participants in the control group and 58.3% of TCOT–treated study participants). The MWT healing rate was calculated as the mean of 6 published DFU studies.[21-26] The TCOT healing rate was based on the mean of 2 unpublished case series performed in US and Canadian clinics. Under the above assumptions, 48 study participants per treatment group, totaling 96 study participants in the study, were required to meet the 2-sided Type I error rate of 0.05 and 80% power; anticipating a 40% drop-out rate brought the recommended sample size to 160.

The primary analysis was conducted using the intent-to-treat (ITT) population, defined as the set of randomized study participants who had at least 1 post-randomization efficacy assessment for wound healing. A secondary analysis was based on the per-protocol (PP) population, which consisted of study participants in the ITT population who were not associated with a major protocol violation. Safety assessments were made with the safety population, defined as any study participant receiving treatment after randomization. Continuous variables (age, weight, height, ABI, white blood cell count, creatinine, and HbA1c; and wound area, volume, and duration) were summarized as mean ± standard deviation (SD). Categorical variables (gender, race, diabetes type, neuropathy, smoking, previous amputation, and use of offloading) were summarized as count and percentage with categories as relevant.

Two (2) methods were used to assess treatment efficacy based on the scale and component summary scores derived from the SF-12v2. Analysis of covariance (ANCOVA) was used to compare final visit scores between the treated and the control groups. Baseline score was included as a covariate in the model and treatment arm was included as a fixed effect. Statistical tests were conducted to test whether final±mean

Table 2. Patient baseline demographic data and wound variables

Variable	Control group (n = 61)	TCOT[a] group (n = 61)
Age (years)		
Mean±SD[b]	58.8±9.4	58.6±12.31
Range	34.0–79.0	27.0–85.0
Gender		
Male, n (%)	47 (77)	43 (71)
Female, n (%)	14 (23)	18 (30)
Race		
White non-Hispanic, n (%)	33 (54)	38 (62)
White Hispanic, n (%)	13 (21)	15 (25)
African-American, n (%)	7 (12)	5 (8)
Other non-Hispanic, n (%)	3 (5)	1 (2)
Other Hispanic, n (%)	5 (8)	2 (3)
Weight (lb)		
Mean±SD[b]	229.3±58.1	212.6±62.9
Range	108.0–365.0	87.0–393.0
Height (inches)		
Mean±SD[b]	69.3±3.9	68.7±5.4
Range	62.9–77.0	50.0–76.0
HbA1c (%)		
Mean±SD[b]	7.9±1.7	8.0±1.7
Range	4.1–11.9	4.0–12.0
Ankle brachial index		
Attainable, n (%)	49 (80)	50 (83)
Mean±SD[b]	1.0±0.2	1.0±0.2
Range	0.6–1.5	0.6–1.6
Unattainable, n (%)	12 (20)	11 (18)

Table 2. Patient baseline demographic data and wound variables *continued*

Variable	Control group (n = 61)	TCOT[a] group (n = 61)
White blood cell count		
Mean±SD[b]	7.8±1.9	7.9±21.
Range	4.4–11.7	4.6–12.4
Creatinine (mg/dL)		
Mean±SD[b]	1.2±0.6	1.1±0.5
Range	0.4–3.1	0.3–2.9
Type of diabetes		
Type 1, n (%)	10 (16)	6 (10)
Type 2, n (%)	51 (84)	55 (90)
Neuropathy prevalence, n (%)	46 (75)	49 (80)
Smoking incidence		
Active, n (%)	12 (20)	3 (5)
Past, n (%)	19 (31)	20 (33)
Never, n (%)	30 (49)	38 (62)
Previous amputation, n (%)	2 (3)	2 (3)
Using offloading, n (%)	53 (87)	53 (87)
Wound area (cm^2)		
Mean±SD[b]	2.3±1.7	2.0±1.7
Range	0.4–8.9	0.6 –8.7
Wound volume (cm^3)		
Mean±SD[b]	0.9±1.3	0.7±1.5
Range	0.0–8.9	0. –8.5
Wound duration (weeks)		
Mean±SD[b]	14.9±12.5	17.7±12.8
Range	5.0–50.0	4.0–50.0

[a]TCOT: transdermal continuous oxygen therapy; [b]SD: standard deviation; [c]HbA1c: glycated hemoglobin

Table 3. Location of wounds on foot

Location	Control group		TCOT[a] group	
	n (%)	Plantar, n (%)	n (%)	Plantar, n (%)
Front	29 (48)	27 (44)	37 (61)	32 (53)
Medial	17 (28)	11 (18)	13 (21)	8 (13)
Heel	11 (18)	9 (15)	8 (13)	8 (13)
Ankle	4 (7)	0 (0)	3 (5)	0 (0)
Total	61 (100)	47 (77[b])	61 (100)	48 (79[b])

[a]TCOT: transdermal continuous oxygen therapy; [b]Percentage equivalent to the percentage of plantar wounds that make up the total wounds

scores adjusted for baseline scores differed significantly (*P* value set at .05) between the active and control groups. In addition to significance testing, Cohen d effect sizes for standardized mean differences were calculated as a way to interpret the magnitude and direction of the difference in the adjusted final SF-12v2 scores between groups.

Efficacy was also assessed using categories of change derived for SF-12v2 physical and mental component scores. Each patient's final visit SF-12v2 physical and mental component score was categorized as "better," the "same," or "worse" than their baseline SF-12v2 score according to the magnitude and direction of the difference in scores between baseline and final visit assessments. In addition, a chi-square test was conducted to test whether the distribution of participants in the 3 categories differed between the study and control groups.

The primary endpoint was defined as complete wound closure by week 12 and was analyzed using chi-squared tests. Time to complete closure was analyzed using Kaplan-Meier analysis in conjunction with the log-rank test. Subgroup analysis was conducted by age using 65 years as the break point.

Adverse events (AEs) were classified by system organ class and preferred term according to MedDRA dictionary (Version 12.0). All AEs that occurred on or after the date of first application of clinical trial treatment were listed and summarized, using frequency counts and percentages, by treatment group. AEs were organized as:

- Overall (regardless of severity or relationship to treatment);
- By severity grade (mild, moderate, or severe); or
- By relationship to clinical trial treatment according to the mapping scheme below:
  - o Potentially related: included all AEs with a relationship rating of "definitely," "probably," or "possibly";
  - o Unlikely/not related: included all AEs with a relationship rating of "unlikely" or "unrelated"; or
  - o Unknown.

Serious adverse events (SAEs) were indicated by the investigator as being serious from the question, "Is this considered serious?"

Table 4. Adverse events in the safety population

Event	Control group (n = 66)		TCOT[a] group (n = 64)		*P* value[b]
	N	%	N	%	
Secondary amputation	1	25	0	0	
Edema	4	6	2	3	0.681
Study wound infection	10[c]	15	3[d]	5	0.086
Cellulitis	6	9	1	2	0.119
Osteomyelitis	0	0	1	2	
Staphylococcus infection	1	2	0	0	
Infected skin ulcer (non-study wound)	4	6	4	6	1.0
Streptococcal bacteremia	0	0	1	2	
Abscess	0	0	2	3	
Gas gangrene	1	0	0	0	
Total	27		14		

[a]TCOT: transdermal continuous, oxygen therapy; [b]Fisher's exact test; [c]1 mild, 6 moderate, 3 severe; [d]1mild, 1 moderate, 1 severe

Results

A total of 183 patients provided informed consent and were screened, of which 53 were excluded due to screen failures (see Figure 1). Of the 130 study randomized participants, 30 dropped out (12 in the TCOT arm and 18 in the control arm). Causes for discontinuation from the study included patient withdrawal, noncompliance, AEs, and study participants found ineligible after enrollment (see Figure 1). Of the 130 study participants enrolled into the study safety population, 128 were classified as ITT: 65 in the TCOT group and 63 in the control group, with 61 from each group in the PP population.

No major statistical differences were found in demographics between the TCOT and control groups; specifically, health questionnaire and pain scale scoring showed no statistical differences between the control and treatment groups (see Table 2). The mean age of the study population was approximately 59 (range 28–85) years; the study participants were predominantly male (74%) and Caucasian (81%). Although study participants with plantar ulcers received offloading boots, compliance levels were difficult to assess. All study participants were treated as outpatients in wound clinics. Table 3 shows the distribution of wound location; 77% of the study participants in the control group and 79% of study participants in the TCOT group had plantar wounds. The average wound area for the control group was 2.3 ± 1.7 cm^2 (range 0.4–8.9 cm^2) and for the TCOT group was 2.0 ± 1.7 cm^2 (range 0.6–8.7 cm^2).

Table 5. Laboratory test results from baseline to end of treatment

Laboratory test	Control group		Transdermal continuous oxygen therapy (TCOT) group	
	Baseline	End of treatment	Baseline	End of treatment
White blood cells (103/uL)				
Tests from each group (n, %)	39 (64)	39 (64)	40 (66)	40 (66)
Mean SD[a]	8.0±1.87	7.6±1.7	7.6±2.0	7.4±2.2
P value[b]		0.1949		0.3750
Creatinine (mg/dL)				
Tests from each group (n, %)	39 (64)	39 (64)	42 (69)	42 (69)
Mean SD[a]	1.3±0.6	1.4±0.7	1.±0.5	1.1±0.5
P value[b]		0.0520		0.8330
HbA1c (%)[c]				
Tests from each group (n, %)	39 (64)	39 (64)	43 (71)	43 (71)
Mean SD[a]	8.1±1.7	8.0±1.7	8.0±1.7	8.4 ±2.1
P value[b]		0.4417		0.1195

[a]SD: standard deviation; [b]Wilcoxon rank test; [c]HbA1c: glycated hemoglobin

Table 6. Causes of transdermal continuous oxygen therapy (TCOT) device malfunction and their resolution

Device malfunction	Control	TCOT	Cause	Resolution
Devices dispensed	266	255		
Total malfunctions	6.0%	3.90%		
Luer breakage	3.8%	3.1%	Flaw in Luer design	A new, strengthened Luer design was introduced, after which no Luer breakages occurred
Fluid back-up	0%	0.4%	Improper offloading	Patient instructed to offload properly
LED indicator light	1.1%	0.4%	Possible failure to turn on completely	An investigation was conducted; no root cause found
Cannula disconnected	1.1%	0%	Cannula not tightened enough	Patient and physician instructed on proper tightening of cannula

In the ITT population, among the TCOT treated patients, 35 out of 65 completely healed their wounds and 31 out of 63 healed in the control arm ($P = .4167$), indicating a lack of statistical significance of the results. In the 65 years or older group, 15 out of 19 in the TCOT group and 8 out of 16 in the control group were healed by week 12 ($P = .0723$). Among the TCOT-treated study participants in the PP population, 34 out of 61 (56%) achieved complete wound healing, while 31 out of 61 (49%) in the control group achieved complete wound healing (see Figure 2). The Kaplan-Meier graph in Figure 2 shows an increase in the healing rate starting at week 3 in the TCOT group; the higher healing rate is seen until week 10, after which both treatments converge ($P > .05$). In the ≥65 years subgroup, in the PP analysis of DFUs, 14 out of 17 patients in the TCOT group (82%) healed versus 8 out of 16 study participants (50%) in the control arm ($P = .049$). Figure 3 shows the comparison plots for the Kaplan-Meier analysis of patients ≥65 years age.

The median time to complete closure estimated from the Kaplan-Meier analysis for the PP population was 63 days for the TCOT group and 77 for the control group (not statistically significant). In the PP analysis for the ≥65 age subgroup, the median time to closure was 35 days for the treated and 70 days for the control group ($P = .139$ based on log rank test).

Safety analysis. A total of 25 SAEs (13 control, 12 TCOT) occurred and all were unrelated or unlikely related to the device. A similar number of AEs (55 and 53) occurred in the control group and TCOT group, respectively. Of these, 1 was probably related (a wound was caused by the offloading boot) and 3 were possibly related to the TCOT device. The remaining AEs were all unrelated or unlikely related.

Fewer infections were observed in the TCOT group (3, 5%) compared with the control group (10, 15%), but the differences were not statistically significant (see Table 4). Similarly, cellulitis incidents were more frequent in control group (6, 9%) compared with the TCOT group (1, 2%), but again these differences were not significant. For all other events, no significant differences were observed.

Results of laboratory assessments for both the groups are summarized in Table 5. No significant differences between the 2 groups were noted.

Of the 266 devices dispensed to the control group, 6% prematurely failed for various reasons; out of the 255 dispensed to the TCOT group, 3.9% prematurely failed. Table 6 lists the causes of malfunction and the resolution.

Discussion

This is the first double-blind RCT describing the use of TCOT for the treatment of DFUs. Because this was a Phase II study, the inclusion and exclusion criteria were designed to exclude any patients with comorbidities. These criteria made recruitment difficult; for example, in a diabetic population, it is difficult to find patients ≥ 65 years old without any kidney or vascular issues. This restriction delayed the recruitment process considerably and ultimately the condition of equal enrollment regarding the age strata could not be fulfilled.

The percentages of healed wounds in the TCOT and control groups for the ITT and the PP population were similar, but the closure rate of the control group was much higher than observed for standard care in other DFU RCT studies[18-23] (~28%). This may indicate that either SC was much better in the current study than these trials or the current population had smaller, less severe wounds on average with patients who had fewer comorbidities that could have affected healing. While an occlusive dressing was used, secondary dressings were utilized to manage exudate. Clinically speaking, a moist wound environment was comparable in both groups. It is worth noting that in calculating the sample size for the trial, a standard 30% healing rate for DFU was used based on 6 different prior publications.[22,27-31] In this study, approximately 50% of wounds healed in both treatment arms. Safety analysis demonstrated no significant differences in the AEs between the 2 arms; the TCOT device was safe.

Limitations

A major limitation of this study is that the cohort was not representative of multiple comorbidities or larger wound sizes found in the previous, smaller unblended study.[19] Other limitations were patient recruitment concerning covariate stratification, the small size of the wounds in this study, and the short run-in period. The data also suggest older patients may benefit more from TCOT, although age may be a proxy for more severe comorbidities, such as duration of diabetes and complications from longer wound duration.

No major issues were noted regarding how the study was conducted, the safety, or the loss to follow-up (found acceptable).

Conclusion

The TCOT device tested in a well-conducted, blinded, RCT in conjunction with SC does not appear to offer added benefit over SC in the healing of small, nonsevere DFUs in relatively healthy patients. However, the device may offer a greater benefit to older patients. Future research should concentrate on patients with larger, more severe wounds and more severe comorbidities to determine whether TCOT would benefit the healing of their wounds. ■

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