# Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial

**Objectives:** Perfusion and blood oxygen levels are frequently insufficient in patients with hard-to-heal wounds due to poor circulation, vascular disruption and vasoconstriction, reducing the wound's capacity to heal. This study aimed to investigate the effect of topical oxygen on healing rates in patients with hard-to-heal diabetic foot ulcers (DFUs) (i.e., non-responsive over four weeks).
**Method:** This multicentre, open-label, community-based randomised clinical trial compared standard care (SOC) with or without continuous topical oxygen therapy (TOT) for 12 weeks in patients with DFUs or minor amputation wounds. SOC included debridement, offloading with total contact casting (TCC) and appropriate moisture balance. Primary endpoints were the number of patients to achieve complete wound closure and percentage change in ulcer size. Secondary endpoints were pain levels and adverse events.
**Results:** For the study, 145 patients were randomised with index ulcers graded Infectious Diseases Society of America (IDSA) 1 or 2, or Wagner 1 or 2. In the intention-to-treat analysis, 18/64 (28.1%) patients healed in the SOC group at 12 weeks compared with 36/81 (44.4%) in the SOC plus TOT group (p=0.044). There was a statistically significant reduction in wound area between the groups: SOC group mean reduction: 40% (standard deviation (SD) 72.1); SOC plus TOT group mean reduction: 70% (SD 45.5); per protocol p=0.005). There were no significant differences in changes to pain levels or adverse events.
**Conclusion:** This study suggests that the addition of TOT to SOC facilitates wound closure in patients with hard-to-heal DFUs.
**Declaration of interest:** Inotec AMD Ltd., UK funded SerenaGroup to design, conduct and monitor the study. Inotec AMD Ltd. acted as the study sponsor. The authors have no other conflicts of interest to declare.

**chronic wound • clinical trial • diabetes • diabetic foot ulcer • dressing • hard-to-heal wound • infection • topical oxygen therapy • total contact casting • ulcer • wound**

Recent literature recognises the increased numbers of patients presenting with complications associated with diabetes, such that diabetic foot disease is now considered the tenth leading cause of global disease burden and disability.[1] Many of these wounds are complex hard-to-heal wounds that take extended periods of time to heal despite specialist care in multidisciplinary settings, and the management of such wounds presents clinicians with a challenge from both the clinical and cost-effectiveness perspectives.[2] In this context, it is understandable that clinicians are looking for innovations in wound healing to support their patients, particularly those with hard-to-heal wounds.

Due to its key role in facilitating all stages of the wound healing process, from haemostasis through to re-epithelialisation, the use of oxygen in wound healing is not new, and can be traced back to the 1960s, with early work focusing on the role of hyperbaric oxygen.[3] It is only recently that there have been enough studies in the field of topical oxygen therapy (TOT) that a systematic review of the evidence could be undertaken. A systematic review, focusing on diabetic foot ulcers (DFUs), included five studies (with a total of 80 patients) of which only two were randomised clinical trials.[4] The authors of the review concluded that TOT facilitates wound healing, particularly in less serious ulcers. As Vas and Pananas[5] highlighted in their editorial, the scope of this review excluded some other relevant studies. Driver et al.,[6] in a study of 130 patients, found no difference in the healing rates for patients receiving standard care (SOC) with or without TOT, while two studies have shown positive results in favour of TOT. Niederauer et al.,[7] in a study of 146 patients, demonstrated a two-fold improved rate of healing at 12 weeks when using continuously diffused TOT. Frykberg et al.[8] concluded that multimodal TOT applied with pressure, varied cyclically, can lead to even higher healing rates.

Innovators have also investigated ways of allowing patients to be ambulatory and receive continuous

**Thomas E Serena**,[1] MD, FACS, FACHM, MAPWCA, CEO and Medical Director*; **Neal M Bullock**,[2] DPM, Royal Research Investigator; **Windy Cole**,[3] DPM, Director of Wound Care Research, College of Podiatric Medicine; **John Lantis,**[4] MD, Professor of Surgery and Vice Chair of Department of Surgery; **Lam Li,**[5] MD, President; **Sarah Moore,**[1] RN, Vice-President of Research; **Keyur Patel,**[6] DO, President; **Matthew Sabo,**[7] DPM, President; **Naz Wahab,**[8] MD, President of Wound Care Experts; **Patricia Price,**[9] PhD, Emeritus Professor
***Corresponding author email:** serena@serenagroups.com
**1** SerenaGroup Inc., Cambridge, MA, US. **2** Royal Research Corp., Pembroke Pines, FL, US. **3** Kent State University, Cleveland, OH, US. **4** Mt. Sinai West and Icahn School of Medicine, New York, NY, US. **5** Heal Foundation Tulsa, OK, US. **6** D&P Inc, Pittsburgh, PA, US. **7** Foot and Ankle Wellness, Butler, PA, US. **8** Wahab Consulting and Research, Las Vegas, NV, US. **9** Cardiff University, UK.

24/7 treatment with a TOT device in situ. A recent pragmatic review of its use in a clinical setting on 100 patients,[9] concluded that 57% of DFUs and 47% of venous leg ulcers (VLUs), previously defined as hard-to-heal (mean duration >15 months), went on to heal. Two small studies have investigated the use of this particular technique in patients with DFUs (n=20 in a comparative study;[10] n=10 in a prospective review[11]) and concluded that the device was extremely promising but called for further larger scale trials to be undertaken. Consequently, the present study was designed to investigate the effect of continuous TOT on healing rates in patients with hard-to-heal ulcers (non-responsive to standard treatment over four weeks) in combination with SOC.

## Method

This was a multicentre, open-label, randomised clinical trial conducted in 19 outpatient centres, geographically spread across the US. The primary objective of the study was to investigate the healing rates of hard-to-heal DFUs, which had been unresponsive to treatment for four weeks, when treated with TOT and SOC, compared with SOC alone. The study was performed in accordance with US and international standards of Good Clinical Practice, the Declaration of Helsinki, and was approved by appropriate ethics committees (Western Institutional Review Board (WIRB) No: 20191085) and registered at Clinicaltrials.gov (NCT03905863). All patients provided written informed consent and were reimbursed $100 USD per visit for transportation costs.

### Patient inclusion criteria

- Adult patients (≥18 years) with at least half of patients ≥65 years
- At least one DFU or minor amputation, classified by the Infectious Disease Society of America (IDSA)[12] as grade 1 or 2, or Wagner 1 or 2, with a duration >4 weeks but <12 months (by patient report or documented in the medical records) and of a size between 0.5cm$^2$ and 25cm$^2$ (if a patient had more than one active ulcer that fitted the inclusion criteria, then the largest ulcer was identified as the 'index' ulcer)
- Clinical documentation to demonstrate <40% healing in the four weeks before the first treatment visit
- Adequate circulation to the foot, defined as a dorsum transcutaneous oxygen measurement (TCOM) or a skin perfusion pressure (SPP) measurement of ≥30mmHg, an ankle–brachial index (ABI) between 0.7 and 1.3, or a toe–brachial index (TBI) of >0.6 within the three months before the first screening visit
- Target ulcers had to be adequately offloaded with a total contact cast (TCC) (unless an exemption was requested, in which case a fixed ankle walker) for 14 days before randomisation.

### Patient exclusion criteria

- Inability to manage the topical oxygen device
- Wounds that were completely covered in necrotic tissue
- Uncontrolled medical disorders such as serious cardiovascular, renal, liver or pulmonary disease, lupus, palliative care or sickle cell anaemia
- Patients with HbA1c>12.0% (108 mmol/mol)
- Pregnancy
- Child-bearing potential without appropriate contraception
- Lactation
- Participation in another study
- Life expectancy of less than one year
- Treatment of the wound with engineered tissue or other scaffold materials within 30 days preceding the first treatment visit
- Visible signs of improvement in the four weeks before randomisation (defined objectively as a 40% reduction in surface area in the four weeks before enrolment)
- Ulcer healing by >20% in the two weeks before screening (known as the 'historical' run-in period)
- Patients with a history of >2 weeks' treatment with immunosuppressants (including systemic corticosteroids >10mg daily dose), cytotoxic chemotherapy or application of topical steroids to the ulcer surface within one month before the first screening visit, or who received such medications during the screening period
- Patients where the clinician anticipated that there would be a requirement for such medications or hyperbaric oxygen during the course of the study.

### Intervention

Participants were allocated to receive either SOC or SOC plus TOT for a 12-week intervention period.

SOC was defined to include: wound cleansing with sterile water or saline solution, and gentle irrigation of the study ulcer with warm tap water; sharp debridement using a standardised protocol based on TIME principles for wound bed preparation;[13] offloading with a TCC twice in the first week and weekly thereafter (all exceptions had to be agreed by the lead investigator; a fixed ankle walker boot or similar device was acceptable as an alternative, but shoe inserts were not deemed to provide sufficient offloading); moisture balance was provided using a hydrofibre or alginate dressing. In addition, patients were instructed on adherence to the protocol and given instructions to call their clinic if they suspected any signs of an infection.

Those subjects allocated to the SOC plus TOT group were treated using the same protocol as SOC only but were also provided with a Natrox Oxygen Wound Therapy System, consisting of two elements: the Natrox Oxygen Generator and the Natrox Oxygen Delivery System (Inotec AMD Ltd., US) (Fig 1). The oxygen generator is a multiuse battery-powered device which generates oxygen through water electrolysis and delivers a pure oxygen flow rate of 15ml/hour. The oxygen delivery system is a sterile, single-use device which has a web-like design that allows wound exudate to pass through to the secondary dressing while

allowing the diffusion of oxygen across the wound bed. It connects directly to the oxygen generator via a thin, flexible fine-bore tube. While the oxygen delivery device can remain in situ for seven days, it should be changed at each dressing change, based on exudate level or clinical judgement. This is a battery-operated system with a 30-hour battery life; the kit includes two interchangeable, rechargeable batteries. Each participant was advised to charge one battery while the other was in use, as the battery required changing daily. The oxygen generator is worn in a holster that is fashioned around the leg, enabling patients to ambulate.

### Randomisation and sample size

A computer-generated randomisation list was used to randomise patients across all sites in a 1:1 ratio; an envelope system was used to allocate to groups based on the next available envelope in the sequence. Based on performance in previous trials with a similar intervention period, an anticipated dropout rate of 10% was built into the recruitment plan. For an anticipated healing rate of 30% in the SOC and a 55% healing rate in the SOC plus TOT group, with 80% power, alpha set at 0.05 and a dichotomous endpoint (healed versus not healed), 60 subjects were required in each group—giving a target of 120 evaluable subjects. Consequently, the study aimed to recruit 132 subjects in order to achieve 120 evaluable subjects at the end of the study; withdrawal rates were closely monitored to allow for additional recruitment to ensure a balanced number of participants across the groups.

### Study procedure

Participants initially underwent screening whereby historic documentation was investigated to confirm the rate of healing in the previous two weeks; if all other inclusion criteria were met and the patient had a healing rate of <20% reduction in wound size, following written consent, the patients could enter the two-week run-in period, whereby all patients were allocated to the SOC protocol. At the baseline visit, if all inclusion and exclusion criteria were still applicable and the wound had not reduced in size by >20%, the patient was randomised and baseline data were collected, including assessment of infection status, and wound pain intensity using a 0–10 anchored analogue scale (where 0=no pain and 10=worst possible pain).

Patients were asked to attend clinic on a weekly basis (±3 days) for up to 12 weeks, when wounds were reassessed and photographed, and a record was kept of any additional wounds that had developed. Adverse events were recorded and reported in line with standardised procedures. If an infection developed after randomisation and allocation to treatment, then the infection was recorded as an adverse event with the site investigator providing treatment with topical antimicrobials and/or oral antibiotics: patients were allowed to remain in the study unless an alternative treatment was deemed clinically necessary.

**Fig 1.** Topical oxygen wound therapy system and components

Patients were recruited from the beginning of June 2019 to the end of June 2020. During the recruitment period, the COVID-19 pandemic was declared by the World Health Organization. Following a short interruption to the study, those patients screened and recruited from April 2020 were reviewed in clinical settings with additional COVID-19 safety measures in place to ensure full compliance with state and federal requirements.

### Study endpoints, data monitoring and statistical analysis

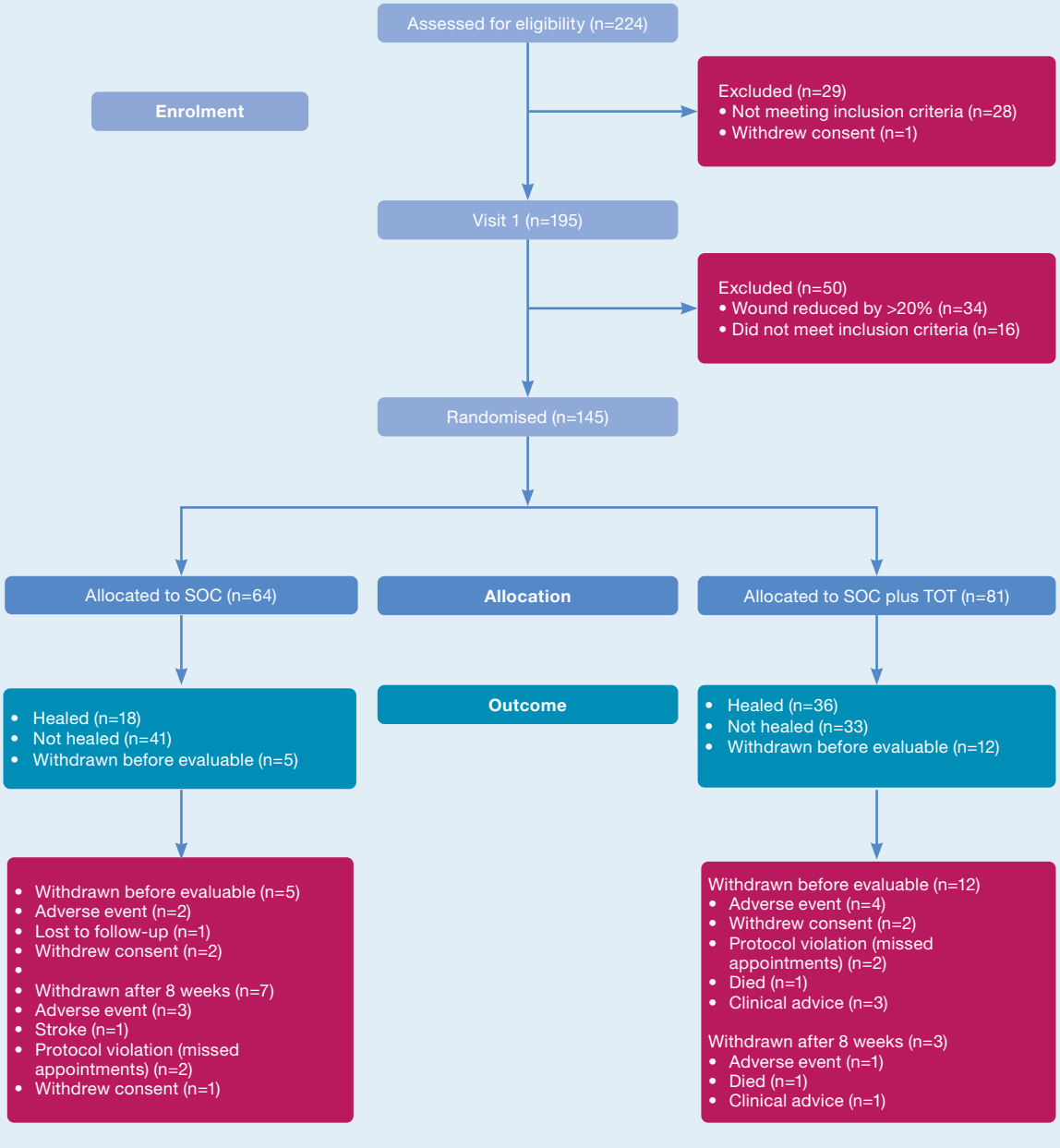
The primary endpoints were the number of wounds that achieved complete wound closure during the 12-week study and the percentage change in ulcer size at 12 weeks from baseline wound area measurement. Photographic wound evaluation and measurements were conducted using an AI-driven computerised planimetry imaging system (Tissue Analytics, Inc., US).[14] This system obtained both two-dimensional (2D) and three-dimensional (3D) assessments of the wound

**Table 1. Baseline characteristics of participants**

| Baseline characteristic | SOC (n=64) | SOC plus TOT (n=81) |
|---|---|---|
| **Age at inclusion, years** | | |
| Mean±SD | 62.69±12.56 | 64.20±14.15 |
| Minimum, maximum | 34, 91 | 33, 93 |
| **Sex** | | |
| Female | 11 | 26 |
| Male | 53 | 54 |
| Not declared | 0 | 1 |
| **Currently use tobacco** | | |
| Yes | 11 | 11 |
| No | 51 | 68 |
| Not declared | 2 | 2 |
| **Diabetes duration, years, (SOC n=60; SOC plus TOT n=76)** | | |
| Mean±SD | 18.33±11.35 | 18.35±13.53 |
| Minimum, maximum | 3, 62 | 1, 55 |
| **Body mass index, kg/m²*** | | |
| Mean±SD | 31.0±7.79 | 30.8±6.83 |
| Minimum, maximum | 19, 51 | 16, 54 |

SD—standard deviation; SOC—standard care; TOT—topical oxygen therapy; *5 patients missing data in each group

**Fig 2.** CONSORT flow diagram; SOC—standard care; TOT—topical oxygen therapy




at each visit through a standardised mobile device; in addition, the lead investigator reviewed all digital images. Secondary endpoints included the changes in pain level associated with the wound, using a visual analogue scale (VAS), the average percentage rate of wound closure and the number of adverse events.

Patients were withdrawn from the study if they withdrew consent, if they were deemed to have been non-adherent to the protocol (agreed on a case-by-case basis with the lead investigator) or if they clinically required a different treatment regimen. Patients who completed eight or more of the weekly assessments were deemed evaluable. Any patient who did not heal or was withdrawn during the study was provided SOC as an ongoing treatment regimen, unless they clinically required a different regimen.

### Data and statistical analysis

Data were recorded on a digital, online clinical report form that allowed records to be completed and verified on a weekly basis by the lead investigator, as the study progressed. The data were analysed independently and

blinded to allocation to group. Statistical analysis was completed using both an intention-to-treat (ITT) and per protocol (PP) models. Categorical variables were analysed using contingency tables (Chi-square) and continuous variables were analysed using either an independent t-test or Mann–Whitney, depending on whether or not they met the criteria for parametric analysis. Statistical analysis was completed using IBM SPSS statistics for Macintosh, Version 25 (IBM Corp, US) with a two-sided p-value of <0.05 considered statistically significant.

## Results

The study initially screened 224 patients for inclusion. This resulted in 195 patients going forward to Visit 1, when 145 patients were randomised to SOC (n=64) or SOC plus TOT (n=81) (Fig 2). More patients were recruited than originally planned in order to ensure that at least 120 patients were evaluable, as permitted in the protocol.

The two groups had similar demographic characteristics at baseline (Table 1), with 79 (54.5%) of all patients >65 years of age. There was a slightly larger mean ulcer area for those in the SOC group, but this was not statistically significant (Table 2). The mean ulcer duration was similar in both groups at around 24 weeks (lower extremity data are only given for the index ulcers in Table 2), with the majority of patients presenting with ulcers graded as IDSA 1 or 2, or Wagner 1 or 2, located in the plantar, dorsal or heel areas. Previous amputation had been experienced by 66 patients, with a slightly higher proportion in the SOC plus TOT group.

All of the 145 patients who were randomised were included in the ITT analysis while the 128 patients who completed eight or more treatment visits were considered evaluable for the PP analysis. Early treatment termination (i.e., before eight treatment sessions; n=17) was due to: withdrawal of consent/unwillingness to adhere to the protocol (n=4); an adverse event (n=6); death not related to the study (n=1); loss-to follow-up (n=1); protocol violations (n=2); and on clinical advice (n=3). There were five withdrawals in the SOC group compared with 12 in the SOC plus TOT group (not statistically significant) before eight weeks. Between week eight and the end of the intervention period, a further 10 patients were withdrawn (SOC: 7; SOC plus TOT: 3); this was due to: withdrawal of consent (n=1); an adverse event (n=4); death not related to the study (n=1); clinical advice (n=1); stroke (n=1); protocol violations (extended hospital stay/missed too many treatments; n=2). Over the 12-week period, 27 patients were withdrawn from the study (SOC:12; SOC plus TOT: 15).

In the ITT analysis, complete healing of the index ulcer was achieved by 18 (28.1%) patients in the SOC group at 12 weeks compared with 36 (44.4%) in the SOC plus TOT group (p=0.044). In the PP analysis, complete healing in the SOC group at 12 weeks was achieved by 30.5% at 12 weeks, compared with 52.2%

**Table 2. Ulcer characteristics at randomisation**

| | SOC (n=64) | SOC plus TOT (n=81) |
|---|---|---|
| **Baseline area, cm²** | | |
| Mean±SD | 3.47±4.12 | 2.86±2.93 |
| Minimum, maximum | 0.5, 21.93 | 0.5, 16.33 |
| **Number of previous ulcers (data missing, n=1 SOC)** | | |
| Mean±SD | 2.32±3.15 | 1.88±1.63 |
| Minimum, maximum | 0, 18 | 0, 7 |
| **Ulcer location, n** | | |
| Ankle | 1 | 2 |
| Dorsal | 12 | 16 |
| Heel | 9 | 9 |
| HIndfoot | 1 | 2 |
| Midfoot | 5 | 6 |
| Plantar | 25 | 34 |
| Toes | 11 | 12 |
| **Ulcer laterality, n (data missing, n=1 SOC)** | | |
| Left | 29 | 43 |
| Right | 34 | 38 |
| **Diabetic foor ulcer (DFU) position, n** | | |
| Anterior | 13 | 21 |
| Lateral | 17 | 21 |
| Medial | 20 | 25 |
| Posterior | 2 | 12 |
| Not recorded | 12 | 14 |
| **Duration of ulcer, weeks** | | |
| Mean±SD | 23.77±17.85 | 24.46±22.62 |
| Minimum, maximum | 4, 114 | 4, 112 |
| **History of previous amputation, n** | | |
| Yes | 25 | 41 |
| No | 38 | 39 |
| Not recorded | 1 | 1 |
| **History of DFU recurrence at study ulcer, n (data missing, n=1 SOC)** | | |
| Yes | 20 | 18 |
| No | 43 | 63 |
| **Infectious Diseases Society of America grade, n (data missing, n=1 SOC)** | | |
| 1 | 49 | 69 |
| 2 | 14 | 11 |
| 3 | 0 | 1 |
| **Wagner grade, n** | | |
| 1 | 48 | 58 |
| 2 | 14 | 22 |
| 3 | 1 | 0 |
| Not recorded | 1 | 1 |
| **Exudate volume, n** | | |
| Heavy/copious | 3 | 8 |
| Moderate | 27 | 22 |
| Light/small | 16 | 24 |
| Minimal | 15 | 18 |
| No exudate | 2 | 8 |
| Not recorded | 1 | 1 |
| **Exudate type, n** | | |
| Purulent | 1 | 1 |
| Sanguineous | 3 | 7 |
| Serosanguineous | 26 | 34 |
| Serous | 30 | 31 |
| None | 3 | 7 |
| Not recorded | 1 | 1 |

SD—standard deviation; SOC—standard care; TOT—topical oxygen therapy

**Table 3. Complete healing outcomes**

| Outcomes ITT | SOC (n=64) n (%) | SOC plus TOT (n=81) n (%) | Total (n=145) n (%) |
|---|---|---|---|
| **All participants** | | | |
| Healed | 18 (28.1) | 36 (44.4) | 54 (37.2) |
| Not healed | 46 (71.9) | 45 (55.6) | 91 (62.6) |
| ITT (n=145) chi squared=4.074, df=1, p=0.044, Cramer's V=0.168 | | | |
| **Outcomes PP** | **SOC (n=59) N (%)** | **SOC PLUS TOT (n=69) N (%)** | **Total = 128 N (%)** |
| **Evaluable participants** | | | |
| Healed | 18 (30.5) | 36 (52.2) | 54 (42.2) |
| Not Healed | 41 (69.5) | 33 (47.8) | 74 (57.8) |
| Per protocol (n=128) chi squared=6.12, df=1, p=0.013, Cramer's V=0.219 | | | |

ITT—intention to treat; PP—per protocol; SOC—standard care; TOT—topical oxygen therapy

**Table 4. Percentage reduction in ulcer area ($cm^2$)***

| All patients (ITT) | SOC (n=64) | SOC plus TOT (n=81) |
|---|---|---|
| Mean±SD | 41.05±69.82 | 46.38±100.24 |
| Minimum, maximum | –160.38, 100 | –487.52, 100 |
| t=–0.362, df=143, p=0.718, mean difference=–5.33; CI=–34.37; 23.81 | | |
| **Per protocol** | **SOC (n=59)** | **SOC plus TOT (n=69)** |
| Mean±SD | 40.44±72.1 | 70.18±45.5 |
| Minimum, maximum | –160.38, 100 | –119.3, 100 |
| t=–2.83, df=126, p=0.005, mean difference=–29.74; CI =–50.54; –8.96 | | |

*A reduction of 100% means that the wound healed; a positive value means that the wound was decreasing in size, all minus values indicate an increase in size; CI–confidence interval; ITT—intention to treat; SD–standard deviation; SOC—standard care; TOT—topical oxygen therapy

**Table 5. Pain assessments**

| All patients (ITT) | SOC (n=64*) | | SOC plus TOT (n=81†) | |
|---|---|---|---|---|
| | **Baseline** | **Final visit** | **Baseline** | **Final visit** |
| Mean±SD | 2.02±2.57 | 0.68±1.43 | 1.81±2.53 | 0.95±1.9 |
| Minimum, maximum | 0, 10 | 0, 6 | 0, 10 | 0, 10 |
| t=1.09, df=140, p=0.278 | | | | |
| **Per protocol** | **SOC (n=58‡)** | | **SOC plus TOT (n=68§)** | |
| Mean±SD | 1.98±2.51 | 0.72±1.47 | 1.85±2.51 | 0.62±1.27 |
| Minimum, maximum | 0, 10 | 0, 6 | 0, 10 | 0,6 |
| t=0.056, df=124, p=0.956 | | | | |

ITT—intention to treat; SD–standard deviation; SOC—standard care; TOT—topical oxygen therapy; *2 missing at final visit; †1 missing at final visit; ‡1 missing at final visit; §1 missing at final visit

in the SOC plus TOT group (p=0.013) (Table 3).

Percentage change in ulcer area was calculated on the basis of area change from the start of the study to the final recorded value (Table 4). Any healed ulcer was recorded as having achieved 100% reduction in area; positive values indicate a reduction in size over the 12-week period, while negative values indicate that the ulcer increased in size. For the ITT analysis, there was no statistical difference in the change in area size. For the PP analysis, there was a statistically significant difference (p<0.005) between the groups, with those in the SOC group achieving a mean reduction of 40% (standard deviation (SD): 72.1) compared with a reduction of 70.1% (SD: 45.5) for those patients in the SOC plus TOT group (p=0.005).

VAS scores were taken weekly. The majority of patients reported no pain, resulting in low mean values at the baseline visit, although a small number of patients reported pain levels towards the higher end of the scale (Table 5). A similar pattern was observed at the final visit; there were no statistical differences between the groups using either the ITT or PP analysis.

Adverse reactions were recorded and reported throughout the study as they occurred (Table 6). In total, there were 32 events reported for the SOC group involving 17 patients (range: 1–4), and 41 events for those in the SOC plus TOT group over 20 patients (range: 1–6). The majority of these were mild or moderate, unrelated to any products used, with the patients remaining in the study. One patient died following an adverse event, but this was not related to the study (one further patient died without a wound-related adverse event). Six patients were discontinued in the trial as a result of an adverse reaction (SOC: 2; SOC plus TOT: 4) within the first eight weeks of the study, with one patient from the SOC plus TOT group and three from the SOC group withdrawn between weeks 9 and 12. Eight patients had an interruption to their time in the study following an adverse event but returned once the issue was resolved.

## Discussion

Millions of people across the globe with DFUs face the possibility of lower extremity amputation and death.[15] Despite advances in therapy, fewer than half of DFUs close in 12 weeks.[16] Recent clinical trials have demonstrated the efficacy of TOT in promoting the healing of DFUs.[7,8] The results presented here corroborate the findings from these earlier studies: the addition of TOT to SOC increased the number of DFUs healed at 12 weeks. Although the overall trial designs are similar, this study had several features that further strengthen the evidence for TOT.

The patients had four weeks of documented nonhealing. The investigators compared the wound measurements at screening to measurements from two weeks before. Patients who had healed by 20% or more during that time were not candidates for the trial. Patients still meeting the inclusion criteria entered two weeks of aggressive SOC: sharp debridement, reduction of bacterial burden and total contact casting. Patients who healed by 20% or more during the two-week run-in period were excluded. As a result, patients who were not candidates for advanced wound care were eliminated from the study. This trial design is consistent with Medicare's coverage policies requiring 30 days of wound care before prescribing advanced modalities, and the inclusion of total contact casting exceeds Medicare's requirements. In addition, 54.5% of the patients enrolled were Medicare beneficiaries: 65 years old or older. In

other words, the patients in this trial mirror the real-life wound care population who will benefit from TOT.

Total contact casting (TCC) is the gold standard for offloading the diabetic foot. It reduces pressure on the plantar foot, decreases patient activity levels and forces adherence with offloading.[17] Despite its advantages, clinical trials rarely use TCCs. The reasons cited vary from the cost of casting to the additional time required to apply and remove a TCC. However, the use of alternative offloading techniques, such as fixed ankle walkers, introduce heterogeneity and potential bias into the trial. This study mandated the use of TCC for plantar ulcers, reducing variability in treatment. The statistically significant difference in healing between SOC and SOC plus TOT is attributable to the addition of topical oxygen.

Topical oxygen may promote DFU healing by several mechanisms: an antimicrobial effect,[18] increasing cellular energy production,[19] promotion of re-epithelialisation,[20] stimulation of angiogenesis[21] and enhancement of collagen synthesis.[22] Topical oxygen increases the oxygen tension in the DFU. As a result, leukocytes that depend on oxygen content to generate superoxide species kill bacteria more efficiently.[18] The cells in the ulcer increase production of the energy-carrying molecule adenosine triphosphate (ATP) in response to the elevated oxygen levels.[19] Re-epithelialisation, angiogenesis and collagen synthesis are also stimulated by the additional oxygen.[20–22]

### Limitations of the study

The study had a high withdrawal rate (18.6%). The multiple comorbidities in patients with diabetes account for a portion of the results. In addition, the latter half of the trial was conducted during the early phases of the coronavirus pandemic, which further contributed to the withdrawal rate. Not surprisingly, patients who did not receive a full course of TOT (for example, patients who withdrew early) did not heal as well as those who completed the study. The lack of blinding may also have added bias to the clinical trial.

**Table 6. Adverse events**

| | SOC (n=32 events) | SOC plus TOT (n=41 events) |
|---|---|---|
| **Severity of adverse events, n** | | |
| Mild | 15 | 22 |
| Moderate | 9 | 12 |
| Severe | 8 | 6 |
| Life threatening* | 0 | 1 |
| **Outcome, n** | | |
| Recovered | 30 | 35 |
| Recovered with sequelae | 0 | 1 |
| Not recovered | 0 | 1 |
| Lost to follow-up† | 2 | 3 |
| Death* | 0 | 1 |
| **Relationship to product, n** | | |
| Unrelated | 30 | 37 |
| Unlikely | 1 | 2 |
| Possibly related | 1 | 1 |
| Probably related‡ | 0 | 1 |
| **Action taken, n** | | |
| Continued | 25 | 30 |
| Interrupted time on study | 2 | 6 |
| Discontinued | 5 | 5 |

*Patient presented with acute hypokalaemic, hypotension and nonischaemic cardiomyopathy; not product related; †Only 1 patient was lost to follow-up before week 8: 1 patient with 4 events was discontinued and final outcome of adverse events is not known; ‡A fall; severity=mild; possibly cast was too big; patient continued; SOC—standard care; TOT—topical oxygen therapy

## Conclusion

This study has demonstrated that TOT can lead to a statistically significant improvement in healing rates in patients with DFUs graded IDSA 1 or 2 or Wagner 1 or 2, that are resistant to healing with SOC alone. There were no statistical differences in the number or type of adverse events related to the use of the product, supporting the use of TOT in an outpatient setting with regular monitoring. Interventions that can support faster healing and maintain care in the community rather than the hospital setting may lead to more cost-effective care in the longer term. JWC

**Acknowledgements**
The authors wish to thank all patients who participated in the trial, particularly those who agreed to participate during the pandemic.

**References**
**1** Lazzarini PA, Pacella RE, Armstrong DG, van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabet Med 2018; 35(9):1297–1299. https://doi.org/10.1111/dme.13680
**2** Game FL, Apelqvist J, Attinger C et al.; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes Metab Res Rev 2016; 32(Suppl 1):154–168. https://doi.org/10.1002/dmrr.2707
**3** Mutluoglu M, Cakkalkurt A, Uzun G, Aktas S. Topical oxygen for chronic wounds: a pro/con debate. J Am Coll Clin Wound Spec 2013; 5(3):61–65. https://doi.org/10.1016/j.jccw.2014.12.003
**4** Nataraj M, Maiya AG, Karkada G et al. Application of topical oxygen therapy in healing dynamics of diabetic foot ulcers: a systematic review. Rev Diabet Stud 2019; 15(1):74–82. https://doi.org/10.1900/RDS.2019.15.74
**5** Vas PR, Papanas N. Editorial and mini-review: topical oxygen therapy for diabetic foot ulcerations: avenue towards new hope? Rev Diabet Stud 2019; 15(1):71–73. https://doi.org/10.1900/RDS.2019.15.71
**6** Driver VR, Reyzelman A, Kawalec J, French M. A prospective, randomized, blinded, controlled trial comparing transdermal continuous oxygen delivery to moist wound therapy for the treatment of diabetic foot ulcers. Ostomy Wound Manage 2017; 63(4):12–28
**7** Niederauer MQ, Michalek JE, Liu Q et al. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicenter study. J Wound Care 2018; 27(Suppl 9): S30–S45. https://doi.org/10.12968/jowc.2018.27.sup9.s30
**8** Frykberg RG, Franks PJ, Edmonds M et al.; TWO2 Study Group. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study. Diabetes Care 2020; 43(3):616–624. https://doi.org/10.2337/dc19-0476
**9** Kaufman H, Gurevich M, Tamir E et al. Topical oxygen therapy stimulates healing in difficult, chronic wounds: a tertiary centre experience. J Wound Care 2018; 27(7):426–433. https://doi.org/10.12968/jowc.2018.27.7.426
**10** Yu J, Lu S, McLaren AM et al. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound Repair Regen 2016; 24(6):1066–1072. https://doi.org/10.1111/wrr.12490 Medline
**11** Hayes PD, Alzuhir N, Curran G, Loftus IM. Topical oxygen therapy

**Reflective questions**

- What role might topical oxygen play in the treatment of hard-to-heal diabetic foot ulcers (DFUs)?
- How important is it to use total contact casting for DFUs?
- How important is it for clinical trial participants to reflect the general wound clinic population?
- What are the advantages of an ambulatory oxygen delivery system in treating patients in the outpatient wound clinic, private physician's office or home healthcare setting?

promotes the healing of chronic diabetic foot ulcers: a pilot study. J Wound Care 2017; 26(11):652–660. https://doi.org/10.12968/jowc.2017.26.11.652
**12** Lipsky BA, Berendt AR, Cornia PB et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012; 54(12):e132–e173. https://doi.org/10.1093/cid/cis346
**13** Dowsett C, Newton H. Wound bed preparation: TIME in practice. Wounds 2005; 1(3):58–70
**14** Budman J, Keenahan K, Acharya S, Brat GA. Design of a smartphone application for automated wound measurements for home care. Iproc 2015; 1(1):e16. https://doi.org/10.2196/iproc.4703
**15** Sen CK, Gordillo GM, Roy S et al. Human skin wounds: A major and snowballing threat to public health and the economy. Wound Repair Regen 2009; 17(6):763–771. https://doi.org/10.1111/j.1524-475X.2009.00543.x
**16** Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. Adv Wound Care 2018; 7(3):77–94. https://doi.org/10.1089/wound.2017.0743
**17** Armstrong DG, Nguyen HC, Lavery LA et al. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care 2001; 24(6):1019–1022. https://doi.org/10.2337/diacare.24.6.1019
**18** Rabkin JM, Hunt TK. Infection and oxygen. In: Davis JC, Hunt TK (eds). Problem wounds: the role of oxygen. Elsevier, 1988:1–16
**19** LaVan FB, Hunt TK. Oxygen and wound healing. Clin Plast Surg 1990; 17(3):463–472. https://doi.org/10.1016/S0094-1298(20)30621-0
**20** Asmis R, Qiao M, Zhao Q. Low flow oxygenation of full-excisional skin wounds on diabetic mice improves wound healing by accelerating wound closure and reepithelialization. Int Wound J 2010; 7(5):349–357. https://doi.org/10.1111/j.1742-481X.2010.00716.x
**21** Gordillo GM, Roy S, Khanna S et al. Topical oxygen therapy induces vascular endothelial growth factor expression and improves closure of clinically presented chronic wounds. Clin Exp Pharmacol Physiol 2008; 35:957–964. https://doi.org/10.1111/j.1440-1681.2008.04934.x
**22** Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet 1972; 135(4):561–567