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ORIGINAL ARTICLE

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A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing

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Abstract

Multiple clinical trials and real-world studies have demonstrated accelerated healing in diabetic foot ulcers (DFU) treated with advanced modalities, such as topical oxygen therapy (TOT). In addition to healing, the durability of wound closure is a crucial long-term endpoint for DFU clinical trials: an advanced treatment that does not confer a reasonable ulcer-free period will have limited clinical benefit and modest economic value. Preclinical studies suggest that DFUs receiving topical oxygen therapy will experience improved quality of healing: increased collagen deposition and angiogenesis. It is postulated that these changes will translate into a more long-lasting closure for ulcers treated with TOT and SOC compared to ulcers treated with SOC alone. At the conclusion of a recently completed randomised controlled DFU clinical trial evaluating the efficacy of TOT and SOC compared to SOC alone, patients with healed ulcers were asked to enrol in a long-term follow-up study. Healed patients completed four questionnaires through text messages or phone calls within 1-year post completion of the trial. Twenty-nine patients consented to participate in the long-term follow-up trial (17 TOT/SOC and 12 SOC). Only seven subjects were lost to follow up (5 TOT and 2 SOC). This is a surprisingly low number when factoring in the disruption caused by the COVID-19 pandemic that continued throughout the entire follow-up period. In the remaining patients, 85% of the TOT patients and 60% of the SOC remained healed at 1 year. There was one major amputation, which occurred in an SOC-treated patient. The numbers in the long-term follow-up were too small to reach statistical significance; however, there is a strong trend toward more durable closure in ulcers treated with TOT.

KEYWORDS

clinical trial, diabetic foot ulcer, topical oxygen, ulcer recurrence

Key Messages

- clinical trials have demonstrated the efficacy of topical oxygen therapy in the treatment of diabetic foot ulcers
- topical oxygen therapy may improve the durability of closure in diabetic foot ulcers
- diabetic foot ulcer clinical trials should include long-term follow-up endpoints

1 | INTRODUCTION

The management of diabetic foot ulcers (DFUs) challenges clinicians across the globe.[1] Despite advances in treatment, real-world studies report that less than 50% of DFUs are healed at 12 weeks.[2] Clinical trials continue to evaluate novel therapies to promote healing; unfortunately, recurrence is common in this population.[3] The high recurrence rate has led clinicians to use the term "remission" to describe the healed diabetic foot.[4] Durability of closure is a key endpoint in clinical trials: an advanced treatment that does not confer a reasonable ulcer-free period will have limited clinical benefit and modest economic value.

Preclinical studies suggest that treatment with topical oxygen produces changes in wound biochemistry that may confer a more durable DFU closure. Topical oxygen induces the expression of vascular endothelial growth factor (VEGF), an important growth factor in stimulating angiogenesis.[5] In addition, oxygen increases collagen deposition and wound tensile strength.[6] The authors postulate that these changes and others will result in a more long-lasting closure for ulcers treated with topical oxygen.

Randomised clinical trials have demonstrated the efficacy of topical oxygen therapy (TOT) in promoting healing in DFUs compared to standard of care (SOC). A randomised double-blind clinical trial showed that continuous diffusion of oxygen (CDO) therapy and SOC resulted in greater healing than SOC alone.[7] A second randomised placebo-controlled trial published in 2020 concluded that pressurised TOT led to higher healing rates than those receiving standard treatment. The patients were followed for a year after completing the trial. At 12 months post healing, 56% of ulcers healed that healed with TOT remained closed compared to 27% of ulcers in the SOC arm.[8] A 2021 randomised controlled trial (NOW.T-001) demonstrated that a CDO topical oxygen led to statistically significant improvement in healing rates of DFUs that were resistant to healing with SOC.[9] The NOW.T-001 trial included year-long durability of healing study. The results of that trial are the focus of this manuscript.

2 | METHODS

2.1 | Study design and overview

The NOW.T-001 randomised clinical trial compared the efficacy of CDO-TOT and SOC to SOC alone in the treatment of recalcitrant DFUs. Subsequent durability of healing study designed to follow patients whose DFUs achieved complete closure during the NOW.T-001 clinical trial received institutional approval as a separate study. Patients that healed by the 12-week visit signed an IRB-approved consent. This trial was conducted during the COVID-19 pandemic; therefore, patients consented via eConsent. Once enrolled, patients completed four questionnaires administered by text message or phone call within 1-year post completion of the NOW.T-001 trial.

The primary objective was to compare the durability of healing (rate of recurrence) of patients treated with TOT and SOC versus SOC alone.

The study population was drawn from the all-randomised population of diabetic subjects who had previously completed the NOW.T-001 RCT and healed by the 12-week endpoint, regardless of whether they received a study device or standard treatment. NOW.T-001 subjects were randomised by a 1:1 scheme across all sites. Table 1 details the inclusion and exclusion criteria for the NOW.T-001 trial.

2.2 | Study procedure

Subjects who completed the NOW.T-001 trial and healed received a text message or phone call at four separate intervals throughout the year following their completion in the NOW.T-001 trial. Text/Call 1 was completed at Month 3 and Electronic Consent was signed and a series of questions related to wound healing status were asked. Text/Call 2 (Month 6), Text/Call 3 (Month 9) and Text/Call 4 (Month 12) asked the same series of questions related to wound healing status.

Subjects answered the following questions related to their wound status:

TABLE 1 Inclusion and exclusion criteria for NOW.T-001

Inclusion criteria
1. Subjects are male or female, 18 years of age or older. At least 50% of the enrolled population must be ≥65 years of age.
2. Subjects with one of the following wounds: A. Diabetic foot ulcer present for greater than 4 weeks (documented in the medical record) but less than 12 months duration if being treated with active SOC. B. Minor amputation wound sites.
3. Subject has clinical documentation of no visible wound improvement after 4 weeks of standard of care. Objectively, less than 40% healing in the past four weeks from the first treatment visit.
4. Study ulcer is a minimum of 0.5 cm^2 and a maximum of 25 cm^2 at the first treatment visit.
5. Subjects' wound score on the ISDA tool is Grade 1 or 2.
6. The subject is able and willing to follow the protocol requirements.
7. Subject has signed informed consent.
8. Adequate circulation to the affected foot as demonstrated by a dorsum transcutaneous oxygen measurement (TCOM) or a skin perfusion pressure (SPP) measurement of ≥30 mmHg; an ABI between 0.7 and ≤1.3, or TBI of >6 within 3 months of the first Screening Visit.
9. Females of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers, or abstinence).
10. The target ulcer has been offloaded for at least 14 days prior to randomization.
Exclusion criteria
1. Subject has a known life expectancy of <1 year.
2. Subject or caregiver is unable to manage the Natrox device (charge and change batteries daily).
3. Subject has ulcers that are completely necrotic or if the clinician feels it is clinically necessary to cover the wound surface in gel or creams that would prevent the transmission of oxygen to the wound surface.
4. Subject has major uncontrolled medical disorders such as serious cardiovascular, renal, liver or pulmonary disease, lupus, palliative care or sickle cell anaemia.
5. Subject currently being treated for an active malignant disease or subjects with a history of malignancy within the wound.
6. The Subject has other concurrent conditions that in the opinion of the Investigator may compromise subject safety.
7. Known contraindications for the Natrox system.
8. Known allergies to any of the Natrox system components.
9. Concurrent participation in another clinical trial that involves an investigational drug or device that would interfere with this study.
10. Index ulcer has reduced in area by 20% or more after 2 weeks of standard of care from the first screening visit (S1) to the TV1/randomization visit.
11. Subject is pregnant or breastfeeding.
12. Subjects with a history of more than two weeks treatment with immunosuppressants (including systemic corticosteroids >10 mg daily dose), cytotoxic chemotherapy, or application of topical steroids to the ulcer surface within one month prior to first Screening Visit, or who receive such medications during the screening period, or who are anticipated to require such medications during the course of the study.
13. Index ulcer has been previously treated with tissue-engineered materials (e.g., Apligraf or Dermagraft) or other scaffold materials (e.g., Oasis, Matristem) within the last 30 days preceding the first treatment visit.
14. Affected extremity requiring hyperbaric oxygen during the trial or within 2 weeks of treatment visit 1.
15. Known HbA1C >12%
16. An ulcer that has visible signs of improvement in the four weeks prior to randomization defined objectively as a 40% reduction in surface area in the four weeks prior to enrollment.
17. An ulcer that has healed by more than 20% in the 2 weeks prior to screening: "historical" run-in period.
18. An ulcer that heals by more than 20% in the "In clinic" run-in period.

1. Has the ulcer on your foot stayed closed? Is there any drainage or blood from the spot?
2. Do you have any new open sores on your foot?
3. Are you still going to the doctor for a wound? If yes, what wound is your doctor treating?

For the purpose of this study, recurrence is defined as an ulcer that emerged in the same area as the previously treated ulcer.

The durability of closure data was compiled and compared over the course of the long-term trial between the group of healed subjects treated with TOT+SOC and SOC in the NOW.T-001 clinical trial. An electronic study case report form (CRF) was the primary data collection instrument for the study. The electronic CRF was completed for each subject enrolled in the clinical study and verified by the Investigator. Statistical analyses consisted of descriptive statistics only.

3 | RESULTS

One hundred and forty-five patients were randomised in the NOW.T-001 clinical trial. In the Intention to Treat analysis, 18 patients healed in the SOC group at 12 weeks (28.1%) compared with 36 in SOC Plus TOT (44.4%%) ($P = .044$). Of the 54 healed subjects, 29 subjects consented to participate in the long-term trial. The enrollment rate was influenced by the COVID-19 pandemic. Of

those 29 subjects, 17 were in the TOT group and 12 in SOC.

Only seven subjects were lost to follow-up (5 TOT and 2 SOC). This is a surprisingly low number when factoring in the disruption caused by the COVID-19 pandemic that continued throughout the entire follow-up period. In the remaining patients, 85% (10/12) of the TOT patients and 60% (6/10) of the SOC remained healed at 1 year.

Adverse events included two recurrences in the TOT group and four in the SOC group. There was one major amputation, which occurred in an SOC-treated patient.

4 | DISCUSSION

Worldwide more than 40 million people suffer from diabetic foot ulcers (DFU).[10] The presence of a DFU alone increases the risk of mortality by 47%.[11] Despite intense research efforts, the development of effective treatment strategies remains elusive.[12] In the United States the Wound Care Collaborative Community (WCCC) has published guidance on endpoints for wound healing clinical trials to improve outcomes. In addition to complete healing, reducing the incidence of recurrence of DFU is an important clinical trial endpoint.

An analysis of 18 clinical studies revealed that on average the risk of DFU recurrence is 40% at 1 year, 60% at 3 years and 65% at 5 years.[3] For this reason, diabetic foot specialists have suggested replacing the term "recurrence" with "remission."[4] Using this term may lead to structured follow-up and better reimbursement for patients with a history of DFUs.

Recent clinical trials have demonstrated the efficacy of TOT in the treatment of DFUs.[7,8] One of these trials included a long-term follow-up study. It revealed that 56% of the DFUs treated with TOT remained healed at 12 months compared to only 27% of ulcers in the SOC arm. The results from this long-term trial similarly demonstrated greater durability of healing with TOT compared to SOC.

There are several limitations of the study including the loss of 19 healed patients that did not consent for the follow-up trial, the small sample size and the number of subjects lost to follow-up (24%). These limitations were largely imposed by the COVID-19 pandemic that negatively impacted the practice of wound care and clinical research across the globe.

Research to date, suggests that topical oxygen may increase the durability of diabetic foot ulcer closure. Larger long-term studies, such as registries, are planned to further investigate these early findings.

CONFLICT OF INTEREST

Dr Al-Jalodi's fellowship is supported by Inotec Inc. the manufacturer of Natrox.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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