Percentage area reduction at week 4 as a prognostic indicator of complete healing in patients treated with standard of care: a post hoc analysis

Abstract: Early indicators of healing provide valuable information on the potential benefit of treatment. In patients with hard-to-heal (chronic) diabetic foot ulcers (DFUs), timely intervention is critical. Ulcers that fail to show measurable progress within four weeks of treatment are considered recalcitrant. These ulcers increase the risk of soft tissue infection, osteomyelitis and lower extremity amputation. A prognostic indicator or surrogate marker allows for rapid evaluation of treatment efficacy and safety. An inverse correlation between a percentage area reduction (PAR) of ≤50% at week 4 and complete healing by week 12 has been previously established; however, the data were derived from a standard of care (SoC) arm of clinical trials that are over a decade old. In this post hoc analysis, data from a large multicentre prospective randomised controlled trial were reviewed to assess PAR at week 4 as a prognostic indicator in patients treated with SoC. Overall, 65.4% (17/26) of patients with PAR >50% at week 4 achieved complete closure at week 12. The receiver operating characteristic (ROC) curve for area reduction by week 4 showed strong discrimination for predicting non-healing (area under the ROC curve: 0.92; p<0.001; positive predictive value: 70.6%; negative predictive value: 87.2%). These findings are consistent with previous studies and support the use of four-week PAR as a prognostic indicator.

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chronic ulcers • clinical decision support • diabetic foot ulcers • hard-to-heal ulcers • percentage area reduction • surrogate endpoints • surrogate marker • topical oxygen therapy • wound • wound care • wound dressing • wound healing

The rising number of people with diabetes portends a public health crisis.[1–3] Patients with diabetes are at risk for complications affecting various organs and systems, including the formation of diabetic foot ulcers (DFUs). DFUs can take months to heal and many ulcers will persist for more than a year.[4,5] An infected DFU is one of the most frequent reasons for hospitalisation in patients with diabetes and the primary cause of more than half of nontraumatic lower limb amputations.[6–9] Delayed healing increases the probability of adverse sequelae.[10]

Effective and timely management of DFUs is critical. Ulcers that fail to show measurable progress, a decrease in surface area of 40–50% within four weeks of treatment, are considered recalcitrant.[11] These ulcers pose a high risk of systemic infection, osteomyelitis and lower extremity amputation.[12,13] There is a robust body of evidence that demonstrates that ulcers that do not heal by 40–50% PAR in four weeks have a low probability of healing at 12 or 14 weeks.[14–16] The four-week timeframe is a recognised surrogate endpoint for healing in DFUs and based on robust research, and has been proposed to the US Food and Drug Administration (FDA) as a primary endpoint in clinical trials by the Wound Care Collaborative Community (WCCC).[14] These findings suggest that published clinical trials have advanced beyond the primary outcomes recognised in the 2006 FDA guidance[14] to include endpoints widely recognised as important for informing clinical decisions and/or improving patient-centred outcomes.[14]

The data that support percentage area reduction (PAR) as a clinical surrogate endpoint were derived by analysing healing rates in control groups in DFU clinical trials. In the original work, Sheehan et al.[15] found that DFUs that did not heal by 53% PAR at four weeks had only a 9% chance of complete closure at 12 weeks. Similar findings were reported by subsequent authors;[16] however, the standard of care (SoC) in DFU clinical trials at the time of these publications differed dramatically from SoC in more recent clinical trials. For example, none of the earlier trials used total contact

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casting (TCC)—the gold-standard in DFU offloading.[17] In addition, the earlier trials did not include a run-in period to ensure that the patients were receiving optimal SoC at the time of enrolment.

Aim

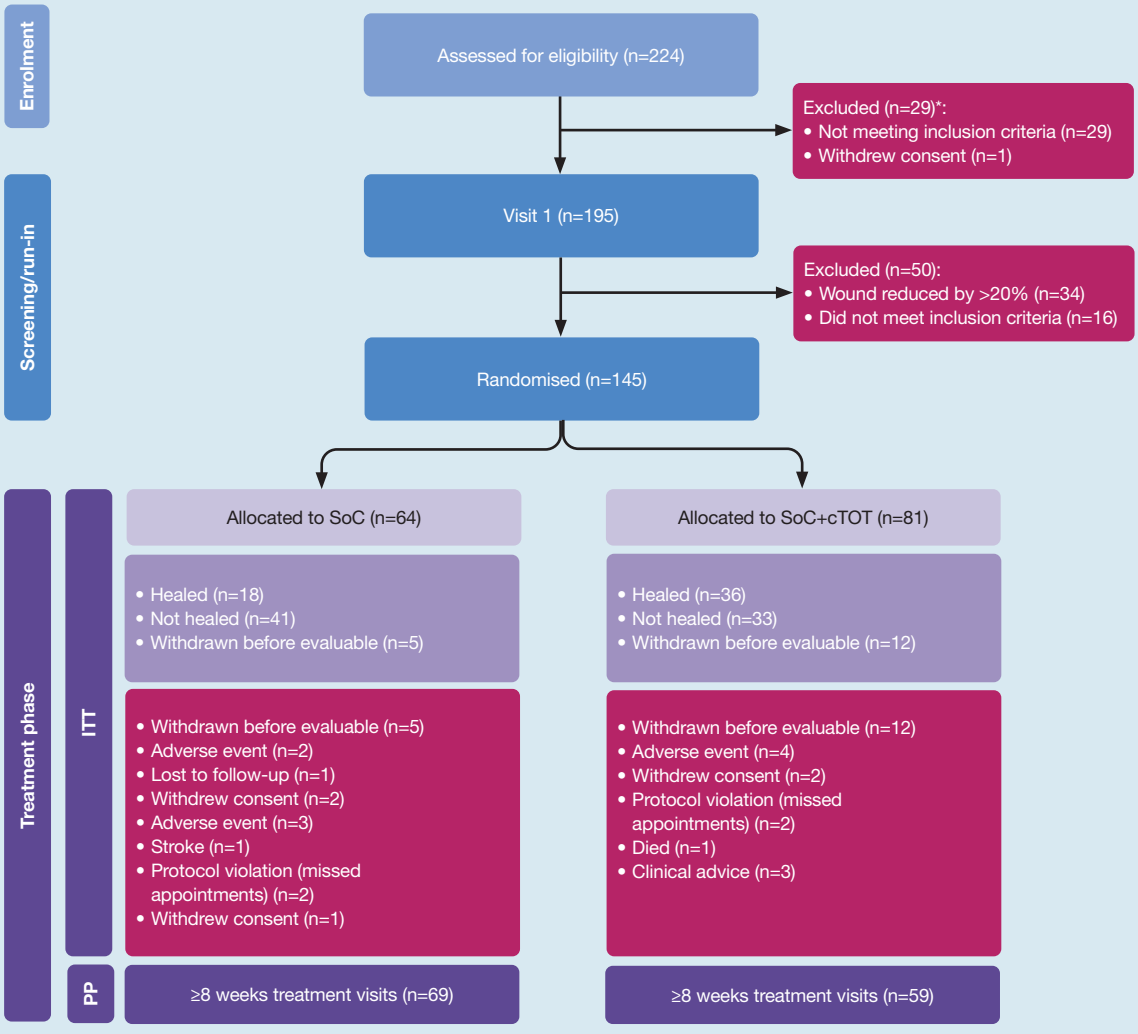
The purpose of this post hoc analysis of the recently conducted Natrox Topical Oxygen Wound Treatment (NOWT) DFU clinical trial[18] was to determine if the four-week surrogate endpoint held true when the wounds in the control arm received modern SoC.

NOWT clinical trial

The NOWT DFU clinical trial,[18] a large multicentre prospective randomised control trial (RCT) conducted between June 2019 and June 2020, evaluated the efficacy of continuous diffusion topical oxygen (Natrox oxygen generator and oxygen delivery system, Inotec AMD Ltd., UK; Fig 1) compared to SoC in the

Fig 1. Continuous topical oxygen therapy device (Natrox Oxygen Wound Therapy; Inotec AMD Ltd., UK)

Fig 2. CONSORT diagram for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial.[18] cTOT—continuous topical oxygen therapy; ITT—intention to treat; PP—per protocol; SoC—standard of care. *One patient counted twice, hence total of 29 excluded



treatment of hard-to-heal (chronic) DFUs. The study had ethical approval (Western Institutional Review Board (WIRB) No: 20191085) and is registered at Clinicaltrials.gov (NCT03905863).

The trial design included a four-week run-in period. If patients' DFUs healed >40% PAR during this time, they were excluded from the trial. The run-in ensured the enrolment of only hard-to-heal DFUs and DFUs that were receiving current SoC. In addition, the SoC included aggressive debridement, offloading with TCC, use of a moisture-balancing dressing (an alginate for exudating ulcers and a foam for ulcers with low levels of exudate) and control of bacterial burden. Table 1 details the inclusion and exclusion criteria.

This post hoc analysis focused only on the SoC arm of the trial; however, in the intention-to-treat (ITT) analysis, 28.1% of the SoC patients healed at 12 weeks compared to 44% in the topical oxygen therapy (TOT) plus SoC group (p=0.044).[18] The ITT and per protocol results are shown in Fig 2.

Methods

In this post hoc analysis, NOWT data were reviewed to assess PAR at week 4 as a clinical prognostic indicator in patients treated with SoC. The CONSORT diagram is shown in Fig 2 and the ulcer demographics are shown in Table 2. All patients included in the study presented with a hard-to-heal Wagner Grade 1 or 2 DFU and had well controlled glucose levels with a haemoglobin A1c <12% and a DFU size between 0.50–25.0cm^2. Adequate circulation to the foot was demonstrated by transcutaneous oxygen measurement (TCOM; ≥30mmHg), ankle–brachial pressure index (ABPI; ≤0.7 and ≤1.3) or other comparable methods. Ulcer beds and periulcer areas were cleansed with normal, sterile saline solution. Offloading was achieved by means of TCC for plantar ulcers and fixed ankle walker boots, or other appropriate means at the discretion of the investigator for non-plantar ulcers.

The data were stratified by 50% PAR at week 4. PAR was computed by dividing the difference between wound surface area (A) at week 1 (W1) and week 4 (W4) by the area at W1:

$$((AW1 - AW4)/AW1) \times 100$$

Complete healing prior to or at week 12 was defined as 100% re-epithelialisation without drainage or discharge. Closure was confirmed by an independent blinded reviewer.

Predictive probability of PAR at week 4 was examined in a logistic regression model. Discrimination was measured by evaluating the area under the curve (AUC) for the receiver operating characteristic (ROC) for the SoC arm. Positive predictive value (PPV) and negative predictive value (NPV) are also reported.

Ethical approval and patient consent

This post hoc analysis did not require additional institutional review board (IRB) approval. The original NOWT study was conducted in accordance with the Declaration of Helsinki, and approved by the Western IRB No: 20191085). IRB-approved informed consent was obtained from all subjects involved in the NOWT study.

Results

The study enrolled a total of 145 patients from 19 wound clinics across the US and Puerto Rico (SoC: n=64; SoC plus TOT: n=81). Patients in both arms were similar in disease characteristics. Both groups had a mean DFU duration of about 24 weeks. The mean area at baseline was recorded at 3.47±4.12cm^2 for patients receiving SoC and 2.86±2.93cm^2 in patients receiving TOT as adjuvant therapy. While the mean DFU area was slightly larger in the SoC group, the difference in area was not statistically significant. In evaluating treatment outcomes, the influence of the treatment arm was evident; Therefore, the analysis was limited to the SoC group.

Previous post hoc analyses evaluated PAR at weeks 2, 4, 6 and 8, and complete closure at weeks 12, 16 or 20.[15,16,19] A few studies have used a logistic regression model with discrimination being measured with the AUC-ROC. The AUC is equivalent to the Concordance (C) statistic, which has also been used to summarise model discrimination. In interpreting these results, it can be understood as the probability that a randomly selected patient with healed outcome will have higher predicted probability or greater area reduction than a randomly selected patient who did not heal.

Overall, 65.4% (17/26) of patients with PAR >50% at week 4 achieved complete closure at week 12 (sensitivity: 66.7%; specificity: 89.1%). The ROC curve for area reduction by week 4 shows strong discrimination for predicting hard-to-heal (Fig 2, AUC: 0.92; p<0.001; PPV: 70.58%; NPV: 87.2%). The difference in area from W1 to W4 is significant in this model (Wald=9.911; df=1; p=0.002. The odds ratio (with 95% confidence interval) is just above 1.

Discussion

The WCCC has identified PAR at four weeks as a valid endpoint for clinical trials in wound healing.[14] It can also serve as a practical guide in clinical decision-making—if a treatment regimen has not resulted in 40–50% PAR healing in four weeks, the patient should be reassessed and a new treatment regimen considered. For patients receiving basic wound care, it may signal the need to employ advanced modalities.

A retrospective analysis on the use of cellular and or tissue-based products (CTP) showed that the average time to advanced therapy in hard-to-heal wounds exceeded 90 days.[20] The data reported previously and the analysis presented here suggest that 30 days is a more appropriate time to use advanced therapy in nonresponding DFUs. The principal author has instituted 'time to advanced therapy' as a quality measure for providers in his practice.

Table 1. Inclusion and exclusion criteria for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial[18]

Inclusion criteria	Exclusion criteria
Subjects are male or female, ≥18 years of age. At least 50% of the enrolled population must be ≥65 years of age	Subject has a known life expectancy of <1 year
Subjects with one of the following wounds: • Diabetic foot ulcer present for >4 weeks (documented in the medical record) but <12 months' duration if being treated with active standard of care (SoC) • Minor amputation wound sites	Subject or caregiver is unable to manage the Natrox device (charge and change batteries daily)
Subject has clinical documentation of no visible wound improvement after four weeks of SoC. Objectively, <40% healing in the past four weeks from the first treatment visit	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
Study ulcer is a minimum of 0.5cm^2 and a maximum of 25cm^2 at first treatment visit (if a patient had >1 active ulcer that fitted the inclusion criteria, then the largest ulcer was identified as the 'index' ulcer)	Subject has major uncontrolled medical disorders, such as serious cardiovascular, renal, liver or pulmonary disease, lupus, palliative care or sickle cell anaemia
Subject's wound score on the Infectious Disease Society of America's tool is Grade 1 or 2	Subject currently being treated for an active malignant disease or subjects with a history of malignancy within the wound
Subject is able and willing to follow the protocol requirements	Subject has other concurrent conditions that, in the opinion of the investigator, may compromise subject safety
Subject has signed informed consent	Known contraindications for the Natrox system
Adequate circulation to the affected foot as demonstrated by a dorsum transcutaneous oxygen measurement or a skin perfusion pressure measurement of ≥30mmHg; an ankle–brachial index between 0.7–≤1.3, or toe–brachial index of >6 within three months of first screening visit	Known allergies to any of the Natrox system components
Females of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers or abstinence)	Concurrent participation in another clinical trial that involves an investigational drug or device that would interfere with this study
Index ulcer has been offloaded with a total contact cast (unless an exemption was requested, in which case a fixed ankle walker) for at least 14 days prior to randomisation	Index ulcer has reduced in area by ≥20% after two weeks of SoC from the first screening visit to the treatment visit 1/randomisation visit
	Subject is pregnant or breastfeeding
	Subjects 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 prior to first screening visit, or who receive such medications during screening period, or who are anticipated to require such medications during the course of the study
	Index ulcer has been previously treated with tissue-engineered materials or other scaffold materials (cellular, acellular, matrix-like products) within the 30 days preceding the first treatment visit
	Affected extremity requiring hyperbaric oxygen during the trial or within two weeks of treatment visit 1
	Known haemoglobin A1c >12%
	An ulcer that has visible signs of improvement in the four weeks prior to randomisation, defined objectively as a 40% reduction in surface area in the four weeks prior to enrolment
	An ulcer that has healed by >20% in the two weeks prior to screening: 'historical' run-in period

This table was first published in Serena et al.[25]

In a retrospective analysis, Snyder et al.[16] pooled control data for PAR at week 1, 2, 3 and 4 from two large multicentre DFU trials to determine best indicator of ulcer closure at week 12. The authors reported a higher AUC-ROC for week 4 (0.91) compared with weeks 1, 2 or 3 (0.71, 0.82 and 0.86, respectively).[16] Another well cited retrospective cohort study by Margolis et al.[20] evaluated PAR at weeks 2, 4 and 8 compared to healed outcome at weeks 12 and 20 of treatment. C-statistic was reported for multiple PAR at different timepoints, with an AUC between 0.73–0.80. Sheehan et al.[15] reported absolute change in area at week 4 to be

Table 2. Patient demographics for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial[18]

Baseline characteristic	SoC (n=64)	SoC+cTOT (n=81)
Age at inclusion, years, mean±SD Minimum, maximum	62.69±12.56 34, 91	64.20±14.15 33, 93
Sex, n		
Female	11	26
Male	53	54
Not declared	0	1
Currently using tobacco, n		
Yes	11	11
No	51	68
Not declared	2	2
Diabetes duration, years*, mean±SD Minimum, maximum	18.33±11.35 3, 62	18.35±13.53 1, 55
Body mass index, kg/m^2†, mean±SD Minimum, maximum	31.00±7.79 19, 51	30.80±6.83 16, 54

*SoC n=60; SoC+cTOT, n=76; †Missing data of five patients in each group; cTOT—continuous topical oxygen therapy; SD—standard deviation; SoC—standard of care. This table was first published in Serena et al.[25]

significantly greater in healing DFUs compared to hard-to-heal DFUs; 58% of the patients with PAR >53% at week 4 healed at week 12 (sensitivity: 91%; NPV: 91%).

Despite the differences in SoC between NOWT and previous DFU trials, the findings in this post hoc analysis are consistent with earlier studies. There is notable heterogeneity in study design, SoC practices and outcome measurement; however, across all studies, the evidence consistently supports the use of PAR at week 4 as a predictor of wound healing at 12 weeks. It has comparable sensitivity and specificity to other tests evaluated as prognostic indicators, including ABPI, TCOM, microvascular oxygen saturation and hyperspectral imaging.[21]

The present study builds on the existing body of evidence supporting PAR at four weeks as a surrogate for DFU healing. It is the first of these studies to mandate TCC for offloading plantar DFUs. The four-week run-in period guaranteed that the DFUs enrolled were hard-to-heal. It also standardised the SoC prior to evaluating four-week healing. Furthermore, prior studies relied on acetate tracings or manual length × width measurements to assess PAR. There is a high error rate with these techniques.[22] The study under review eliminated variability by using digital planimetry for wound assessment and documentation.

Limitations

The principal limitation of this analysis, such as those performed previously, is that it is retrospective. In addition, the data are derived from RCTs. The inclusion and exclusion criteria essential to clinical trial design exclude many patients, such as those with end-stage renal disease or uncontrolled diabetes. Care must be taken in generalising clinical trial findings to everyday practice.

International guidelines for the use of TOT have adopted PAR at four weeks as a guide for the use of this advanced modality.[23] In practice, a DFU that has failed to heal by 40% PAR is a candidate for TOT.

Conclusions

The results of this post hoc analysis confirm previous reports that four-week PAR is a valid surrogate endpoint, predicting healing at 12 weeks. It allows clinicians to discriminate between ulcers that are likely to heal and those that require more advanced therapy. The surrogate endpoint is important in clinical trial design for FDA approval of wound care products. Its use has been recommended by the 2006 FDA guidance document, using an early 'run in' period as an early screening tool to identify rapidly healing wounds.[24] Ample research has demonstrated its broader potential to inform clinical practice and improve patient outcomes. **JWC**

Reflective questions

- How does the addition of topical oxygen therapy with current standard of care promote healing in hard-to-heal diabetic foot ulcers?
- How do different quality measures such as 'time to advanced therapy' and wound percentage area reduction at four weeks impact patient care?
- How can retrospective studies support previously established clinical surrogate endpoints?

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