Interim results for a prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to standard moist wound therapy in the treatment of diabetic foot ulcers

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A R T I C L E   I N F O

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A B S T R A C T

Diabetic foot ulcers (DFU) are common, complex, and often difficult to treat. We examined planned interim data of a prospective, randomized, double-blind multi-center study comparing the clinical efficacy of the TransCu O2® device to standard moist wound therapy (MWT). The therapy, known as continuous diffusion of oxygen (CDO), delivers pure oxygen to the wound at low flow rates, preserves patient mobility, showed significant benefits in animal studies and received FDA clearance in August 2009. We summarize here the results of a per protocol interim analysis of complete wound closure at 12 weeks in a double blind 2-arm clinical trial of 84 subjects randomized 1:1 to Active CDO versus Sham, conducted when 50% of the planned number of subjects completed 12 weeks of therapy (Active 21, Sham 21). We also report treatment comparisons with regard to days to wound closure, study period, and after excluding subjects who experienced fast closure or a small wound (<1.5 cm²) at screen. Complete wound closure at 12 weeks was not significantly associated with treatment per protocol [Active 11 (52.3%), Sham 8 (38.1%), RR 1.38 (95% CI 0.7, 2.7), p = 0.54]. Wound size at Enrollment did not vary significantly with treatment (p = 0.3), days to closure was significantly less among patients who experienced closure in the Active (N = 9) arm relative to those in the Sham arm (N = 3) [mean difference 20 ± 7.9, 95% CI 2.4–37.5, p = 0.03], and complete wound closure at 12 weeks was significantly increased in the Active arm (N = 9) relative to Sham (N = 8) in the second half of the study [Active 77.8%, Sham 12.5%, p = 0.02]. With the numbers available to study in this interim analysis, the absolute performance in the Active arm appeared non-inferior to other reimbursable wound treatment devices.

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Introduction

Oxygen is essential to wound healing and is a rate-limiting factor in tissue repair. Oxygen is a critical component in multiple steps necessary for wound healing including: (1) fibroblast migration and replication [1], (2) collagen production and tensile strength [2], (3) stimulation of angiogenesis [1], (4) promotion of macrophage and chemotaxis [3], (5) antibacterial activity of leukocytes and macrophages [4], and (6) physiologic wound debridement. Since damaged tissue has increased oxygen demands, chronic wounds require intensified oxygen therapy for optimal healing [5,6].

Current wound therapies often employ a moisture absorbent dressing below an occlusive dressing to keep the wound moist, manage drainage and serve as a barrier to bacteria. Since many patients with chronic wounds have impaired blood flow, the poor circulation to the wound dramatically limits tissue oxygenation and can impair healing [7].

Three distinct oxygen-based therapies are currently used to treat chronic wounds: hyperbaric oxygen, topical oxygen, and continuous diffusion of oxygen. Hyperbaric oxygen therapy treats a patient systemically with pure oxygen at elevated pressures. Topical oxygen therapy treats an area directly surrounding the wound at slightly increased pressures. Both of these treatments are typically given for 90 min a day, 4 or 5 days per week. Continuous diffusion of oxygen (CDO) therapy provides continuous oxygen therapy 24 h a day while allowing for full patient mobility.

This study focuses on the use of the TransCu O2® System, which received 510(k) clearance from the FDA in August 2009. The TransCu O2® device provides a therapy known as continuous
Methods

Study design, primary and secondary outcomes

This is a planned interim analysis of a randomized, balanced, double blind, Sham-controlled, parallel group clinical trial evaluating use of the CDO device for diabetic foot ulcers. The planned total sample size was 84 and the estimated total enrollment of the completed study was 110, including subjects who drop. The present analysis is of the first 50% or 42 patients (N = 42) who completed the 12-week treatment phase. The primary efficacy outcome is complete wound closure (yes, no), defined as complete reepithelialization with no drainage. Eligible subjects were those who confirmed to meet all inclusion and none of the exclusion criteria.

This study is also a post market surveillance study designed in consultation with the Center for Medicare and Medicaid Services (CMS). As requested by CMS, the effects of initial wound size and initial rate of closure were investigated. These were defined as:

Initial wound size: the wound area as determined by digital planimetric analysis at the randomization visit.

Initial wound closure rate: the percentage of wound closure between the screening visit and the randomization visit (prior to device application).

The basis for wound size analysis is that smaller wounds are more likely to heal. In theory, the difference between the Active and Sham arms should be larger in larger wounds and smaller in smaller wounds. Furthermore, it has been shown that wounds related to diabetic foot ulcers exhibit a relatively high rate of closure and are likely to close without intervention. Therefore, wounds that exhibit lower initial rates of closure should be more responsive to the use of advanced modalities such as CDO.

Methods

Patients identified as potential candidates for the study were evaluated over a period of 10 days for appropriateness based on study inclusion and exclusion criteria (full criteria available on ClinicalTrials.gov under the identifier NCT 01645891). Those with a DFU present for a minimum of 30 days, yet not more than a year, were eligible for enrollment. Ages were limited to between 30 and 90 years with wound sizes ranging from 1 cm² to 10 cm², as measured by planimetric analysis. All enrolled subjects received a standard wound therapy regimen consisting of wound cleansing, moist wound care, off-loading and, as appropriate, aggressive debridement. After initial screening for eligibility and obtaining informed consent, a patient history and baseline assessment were obtained by the study nurse. Variables assessed included: Ankle/Brachial Index (ABI), wound duration, location and size, loss of protective sensation (determined by 10-g monofilament), and HbA1c. All wounds were classified according to the University of Texas classification for diabetic wounds by a wound specialist based on clinical and laboratory data [9]. All wounds were surgically debrided to a bleeding base as necessary; the number of debridements was not limited but usually debridements were performed once a week before treatment commenced. Subsequent to enrollment, subjects were randomized to either the Treatment Arm (hereafter referred to as Active arm) or the Control arm (hereafter referred to as Sham). All subjects in the Active arm received CDO therapy in addition to standard of care moist wound therapy (MWT) during the Treatment Period and all of those in the Sham arm received Sham units (no oxygen going to wound) and standard of care MWT during the Treatment Period.

All patients were followed for a period of 12 weeks, or until the wound closed, whichever event occurred first, in the Treatment Period. During the Treatment Period, weekly assessments were made of wound size (width, height and depth), degree of reepithelialization of the wound, pain, reduction in odor and the development of granulation tissue. Dressing change frequency depended on the rate of exudate and varied from 2 to 12 events per week. Oxygen wound delivery cannulas were changed with each dressing change.

In order to screen out non-chronic wounds, the study inclusion/exclusion (I/E) criteria required wounds experiencing more than 30% closure between the screening and randomization periods to be excluded from the study. The intent was to find a balance between a short screening period and robust screening criteria to ensure that non-chronic wounds were not included in the study. Upon analysis of the data, it was found that many wounds (>20%) included in the interim analysis were closing at a high rate during this period, indicating that the original 30% criteria may not be sensitive enough to screen out all non-chronic wounds. To improve sensitivity, we restricted the analysis to subjects who experienced (1) wounds that closed more than 50% in the first two weeks (from screen to visit 1), or (2) wounds that closed more than 30% in the first week for those subjects that were randomized on the same day as the screen visit (screen/enroll same day) and we refer to such subjects as those who experienced fast closure between Screen and Visit 1.

To investigate whether there was a combined effect of initial closure rate and wound size on the primary outcome of wound closure, the data were analyzed by wound size in 0.25 cm² segments from all wounds greater than 1 cm² up to the median wound size of 2.28 cm².

As the study progressed, it was found that increased emphasis needed to be placed on proper moist wound therapy principles such as debridement, keeping the wound moist, and the number of dressing changes. Multiple initiatives, including regular conference calls with the overall and site principal investigators and clinical coordinators, were initiated to emphasize these points. As a surrogate for training, we stratified by calendar period to before and after the median visit date (18 July 2013).


**Statistical methods**

Subjects who failed to meet eligibility criteria, withdrew for any reason, or who completed but were not among the first 50% to complete in each arm were excluded. Continuously distributed outcomes were summarized with the sample size, mean, standard deviation, median, first and second quartiles, minimum and maximum, and categorical outcomes were summarized with frequencies and percentages. When contrasting treatment arms with regard to binary outcomes, we report the relative risk (RR) and its 95% confidence interval (CI). The statistical significance of the relation between binary outcomes and treatment arm (Active, Sham) were assessed with Fisher’s exact test. Treatments were contrasted with regard to continuously distributed outcomes with the Mann–Whitney U test and linear models after a log transform. In an analysis of days to closure versus wound closure we used a repeated measures linear model with an autoregressive order one autocorrelation assumption. We used R and SAS for all analyses and graphics. All statistical tests were two-sided with a significance level of 5%. Corrections for multiple comparisons were not applied.

**Results**

As of March 7, 2014, 92 subjects had been screened. Fifty subjects were excluded and the first 50% to complete the study per protocol (N = 42) were included, 21 in the Active and 21 in the Sham arms (Fig. 1). At baseline the two treatment arms were similar with regard to age, ethnicity, sex, and wound size (Table 1).

In the planned interim analysis (Fig. 2A), complete wound closure at 12 weeks was not significantly associated with treatment per protocol [Active 11 (52.3%), Sham 8 (38.1%), RR 1.38 (95% CI 0.7, 2.7), p = 0.54]. A similar pattern was observed after excluding subjects who experienced fast closure between Screen and Visit 1 (Fig. 2B). The effect of wound size on wound closure was initially analyzed above and below the median wound size

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active (N=21)</th>
<th>Sham (N=21)</th>
<th>Total (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.3 ± 01.0</td>
<td>59.2 ± 15.0</td>
<td>58.8 ± 12.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>5 (23.8)</td>
<td>4 (19.1)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (14.3)</td>
<td>5 (23.8)</td>
<td>8 (19.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (28.6)</td>
<td>9 (42.9)</td>
<td>15 (35.7)</td>
</tr>
<tr>
<td>White</td>
<td>12 (57.1)</td>
<td>7 (33.3)</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>Wound area</td>
<td>2.6 ± 1.5</td>
<td>3.4 ± 2.2</td>
<td>3.0 ± 1.9</td>
</tr>
</tbody>
</table>

Fig. 1. Consort diagram.

![Wound closure by treatment arm per protocol and after excluding subjects who experienced fast closure between Screen and Visit 1](image)

![Wound size (cm²) at baseline by treatment arm and wound closure after excluding subjects who experienced fast closure between Screen and Visit 1 (those who closed >50% between Screen and Visit 1 or had the same Screen and Enrollment day and closed >30% between Screen and Visit 1)](image)

**Fig. 2.** (A) Wound closure by treatment arm per protocol and (B) after excluding subjects who experienced fast closure between Screen and Visit 1 (those who closed >50% between Screen and Visit 1 or had the same Screen and Enrollment day and closed >30% between Screen and Visit 1).

**Fig. 3.** Wound size (cm²) at baseline by treatment arm and wound closure after excluding subjects who experienced fast closure between Screen and Visit 1 (those who closed >50% between Screen and Visit 1 or had the same Screen and Enrollment day and closed >30% between Screen and Visit 1) (Active: N = 20, Sham: N = 18).

(Table 2) Further analysis by wound size showed an inflection of relative performance at 1.5 cm². Wound size (cm²) at baseline, (Fig. 3), did not vary significantly by treatment arm (p = 0.3) and this lack of treatment effect did not
vary significantly by complete wound closure (p = 0.25) after excluding subjects who experienced fast closure between Screen and Visit 1 (Table 2).

Among subjects with wound size at least 1.5 cm² and who experienced wound closure and excluding subjects who experience fast closure between Screen and Visit 1 (Active N = 9, Sham N = 3), days to closure increased linearly with wound closure in both arms (Fig. 4) and the average days to closure was significantly less among patients in the Active arm relative to those in the Sham arm (mean difference 20 ± 7.9, 95% CI 2.4–37.5, p = 0.03) and this treatment effect did not interact significantly with wound closure (p = 0.41).

Among subjects with wound size at least 1.5 cm² and excluding subjects who experienced fast closure between Screen and Visit 1, wound closure was not significantly increased in the Active arm (Fig. 5A, p = 0.07). After stratification at the median randomization date (Fig. 5B), wound closure was significantly increased in the Active arm among subjects seen after the median randomization date [Active 77.8%, Sham 12.5%, p = 0.02].

**Discussion**

In this planned interim analysis we found no significant and beneficial treatment effect in the Active arm and so found no statistical basis for stopping the trial early. In a series of exploratory analyses, we found that excluding subjects who experienced fast closure between Screen and Visit 1 and restriction to those with a baseline wound size greater than 1.5 cm² experienced significant and beneficial effects.

When stratified by the primary outcome, the Active arm experienced significantly faster rates of closure relative to the Sham arm. The Active arm experienced significantly shorter times to reach 50%, 75% and 100% closure (Fig. 4). Stratification by primary outcome is the method of analysis performed in multiple peer-reviewed publications to arrive at the 50% closure in one month rule for DFUs [10–12]. The data appears to indicate that the more CDO therapy is needed (larger, more chronic wounds), the better it works.

When restricted to patients seen after the median visit date, significant and beneficial effects were found with regard to the primary outcome. The percentage of subjects experiencing complete wound closure at week 12 was significantly increased in the Active arm relative to Sham. Training apparently affected the primary outcome, with healing significantly increased after the median study randomization date for the Active arm (Fig. 5B). When one considers the design of the study in that both arms are essentially MWT, with one being MWT Plus Oxygen, anything that can effect the delivery of oxygen to the wound will make the Active arm appear more like the Sham (MWT without oxygen). This includes eschar, slough, proper debridement and keeping the wound moist (a dry wound does not allow oxygen in).

This planned interim analysis of CDO therapy on DFUs suggests encouraging trends, both in compatibility or superiority to existing CMS-covered therapies and, in particular, for slower-to-close, larger, chronic wounds. The Active CDO arm versus the Sham arm suggests improved healing in larger wounds and wounds experiencing lower initial closing rates with the numbers available to study at 50% of the planned enrollment. The absolute performance of 53% in the Active arm compares very favorably to published results from other CMS covered therapies (30–52%).

Table 3 shows a comparison of CDO to other advanced treatments in wound closure approved by the United States Center for Medicare and Medicaid Services (CMS), all of which assess wound closure within similar time frames [11]. The non-CDO studies used Kaplan–Meier curves and log-rank testing to assess the significance of treatment efficacy [10,12], whereas the CDO assessed the significance of treatment efficacy with chi-square tests. In this analysis, CDO shows equivalence or superiority to the other advanced treatment modalities. Further experience with the device is likely to reveal that the device benefits patients who need it the most, while the device shows non-inferiority in patients

<table>
<thead>
<tr>
<th>Wound size at enrollment (cm²)</th>
<th>Wound closure (%)</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td>≤2.28</td>
<td>Active 55% (11)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Sham 50% (10)</td>
<td></td>
</tr>
<tr>
<td>&gt;2.28</td>
<td>Active 50% (10)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Sham 27% (11)</td>
<td></td>
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</table>

**Fig. 4.** Days to closure by treatment arm and wound closure (%) among subjects with wound size at least 1.5 cm² and excluding subjects who experience fast closure between Screen and Visit 1 (those who closed >50% between Screen and Visit 1 or had the same Screen and Enrollment day and closed >30% between Screen and Visit 1) and experience closure (Active N = 9, Sham N = 3).
whose wounds are less severe. We look forward to further works that may confirm or refute these data.

Conflict of interest

The preparation of this paper was financially supported by EO2 Concepts.

References


