

# Commentary on A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen therapy (TWO2) in the treatment of chronic diabetic foot ulcers: The TWO2 study

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## Commentary

Topical Oxygen therapy (TOT) in various forms has been used for the treatment of chronic wounds for over fifty years [1-6]. Its effectiveness has been disputed despite many positive clinical and animal reports attesting to its benefits towards promoting wound healing. Various delivery mechanisms have been utilized in this regard including continuous delivery of oxygen (CDO) under low or very low Oxygen tensions or Cyclical Pressurized topical delivery generally within a localized extremity chamber. Hyperbaric Oxygen Therapy (HBOT) proponents have long criticized the ability of TOT to have a meaningful effect on wound repair in the absence of systemic delivery of Oxygen [7]. Despite the many inconsistent wound healing clinical studies of HBOT itself [8-13], most criticisms of TOT, notwithstanding the skepticism mentioned above, are due to an extremely limited number of robust high-quality investigations. We therefore performed a study to assess the efficacy of multi-modality cyclical pressure Topical Wound Oxygen (TWO2) homecare therapy in healing refractory diabetic foot ulcers (DFU) that had failed to heal with standard of care (SOC) alone [14].

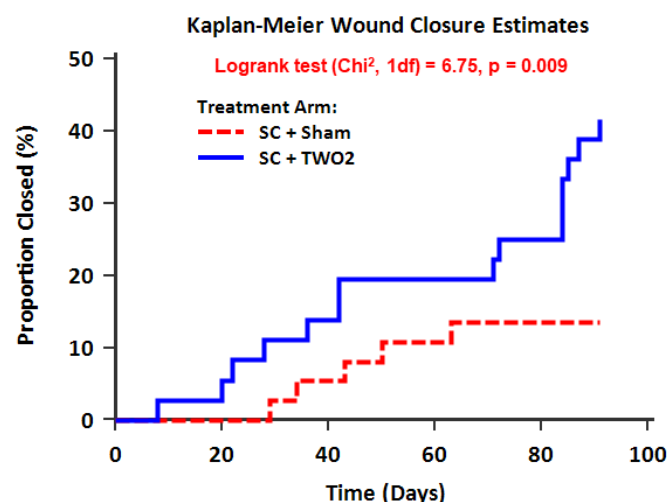
## Research Design And Methods

Patients with diabetes and chronic DFUs that had failed to improve with four weeks of standard clinical care were screened for enrollment. After informed consent the patients entered a two week run-in period of optimal standard of care consisting of uniform offloading, debridement, and dressings. Although 25 percent of these patients healed >30% of their wound area and were subsequently excluded from the trial, eligible subjects were then randomized (double blind) to either active TWO2 therapy or sham control therapy, both in addition to optimal SOC. The primary outcome was the percentage of ulcers in each group achieving 100% healing at 12 weeks. A Group Sequential Design was utilized for the study with three predetermined analyses and hard stopping rules once 73, 146 and ultimately 220 patients completed the 12-week treatment phase.

## Results

At the first analysis point the active TWO2 arm was found to be superior to the sham arm, with a closure rate of 41.7% compared with 13.5%. This difference in outcome produced an odds ratio [OR] of 4.57, [97.8% CI 1.19, 17.57],  $p=0.010$ . After adjustment for University

of Texas Classification (UTC) ulcer grade the odds ratio [97.8% CI] increased to 6.00 [1.44, 24.93],  $p=0.004$ . Cox proportional hazards modelling, also after adjusting for UTC grade, demonstrated more than 4.5 times the likelihood to heal DFUs over 12 weeks compared to the sham arm with a hazard ratio [HR] of 4.66 (97.8% CI 1.36, 15.98),  $p=0.004$ . The Kaplan-Meier curve shown in the **Figure** clearly shows the separation between groups throughout the active phase of the study. Larger wounds (>4cm<sup>2</sup>) also showed significant improvement with the active therapy with an absolute reduction in ulcer area (SD) from baseline of 4.12 (1.51) cm<sup>2</sup> compared to a 1.34 (1.18) cm<sup>2</sup> increase for the sham arm [ $t$  (df) = 2.85 (8),  $p=0.021$ ]. Therapy and Offloading compliance exceeded 95% for both groups.



**Figure 1.** Kaplan-Meier curve showing the separation between study groups throughout the 12-week trial. Solid line represents actively treated group and hashed line indicates the sham treated group

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At 12 months post enrollment, 56% of active arm ulcers were closed compared to 27% of the sham arm ulcers ( $p=0.013$ ) and there was a six fold difference in wound recurrence between groups, favouring the TWO2 treated patients. .

## Conclusions

This sham-controlled, double blind RCT demonstrates that, at both 12 weeks and 12 months, adjunctive cyclical pressurized TWO2 therapy was superior in healing chronic DFUs compared to optimal SOC alone. In contrast to recently reported systemic HBOT studies, this robust double blinded, sham controlled trial provides evidence to support use of this adjunctive cyclical pressurized topical oxygen therapy for chronic DFUs.

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