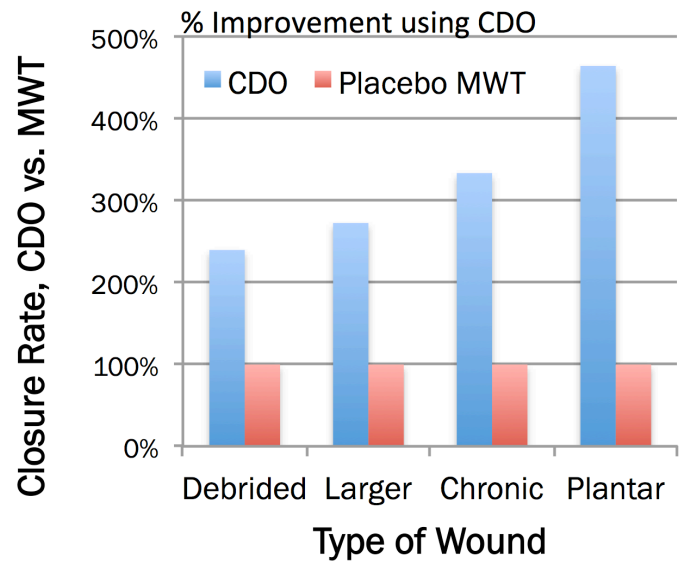


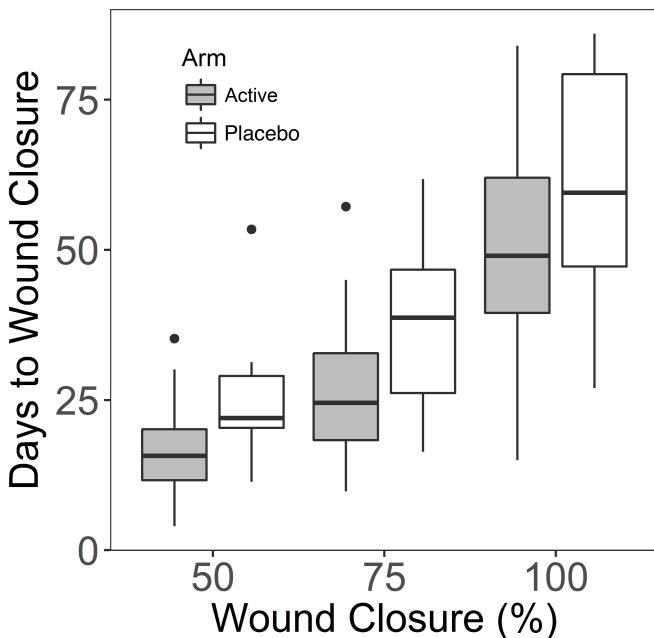
EO₂[®] Clinical Research Summary

Multicenter DFU Study: Results from a **Level 1A Diabetic Foot Ulcer** clinical trial involving **146 patients across 34 sites** show that Continuous Diffusion of Oxygen (CDO) therapy to be **statistically significant** compared to a placebo arm. The study was **published in the Journal of Wound Care** in September of 2018.¹ In the same trial, the effect of debridement as a standard of care on the performance of CDO was **published by Lawrence Lavery et al. in Wounds** in October of 2019. The rigor of this study is rare in the medical device world: a double-blind, prospective, randomly-controlled trial with a placebo and an active arm. Both arms received identical treatment (device, dressings, etc.) and the devices were functional in both arms. However, the

Relative Performance



Rate of Wound Closure



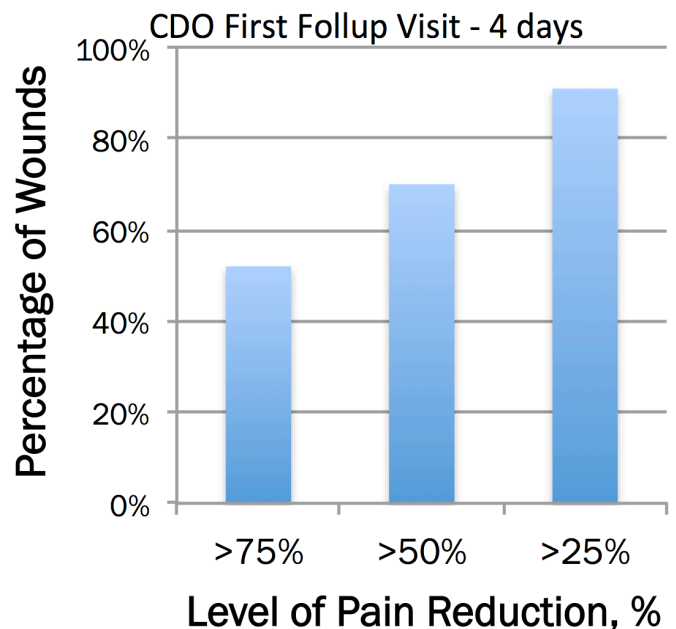
oxygen did not flow to the wound in the placebo arm. In essence, this is on par with a pharmaceutical trial where the patients and clinicians do not know the treatment arm. **CMS cited the study design as the "Gold Standard" for how studies should be designed.**

A significantly higher proportion of people, more than twice as many (204%), healed in the active CDO arm compared to sham (46% vs 22%, $P = .016$). Frequent debridement increased the relative performance to 240% (51% vs 21%, $P = 0.006$). The relative performance became greater as wounds got larger (273%), more chronic (334%) and with weight bearing (plantar, 465%). Patients with CDO experienced significantly faster rates of closure relative to the

placebo ($P < .001$), with the time to 50% wound closure being almost halved with CDO. **Dr. David Armstrong** of the SALSA Clinic, University of Southern California, was the overall principal investigator for this study.

Pain Study: Results from a prospective trial of 20 patients to investigate reduction in pain in patients with 23 chronic lower extremity ulcers were published in Wound Central in September of 2018³. Wounds were found to have pain relief quickly after starting CDO: over half the patients experienced at least a **75% reduction in pain relief by the first follow-up visit (median of 4 days)** and over 90% had noticeable pain reduction (>25%) by the first follow-up visit. All subjects experienced complete pain relief and multiple subjects reported complete pain relief within hours of application of CDO. Subjects also reported being able to cease using narcotics with CDO.

Pain Reduction



December 2019

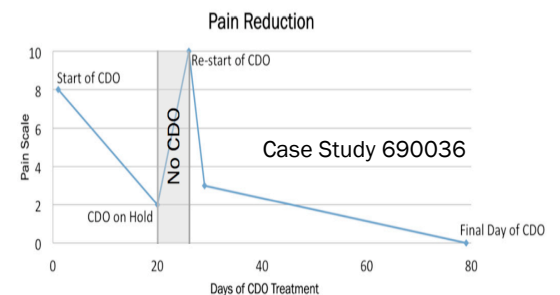


EO₂[®] Clinical Research Summary

Registry: These results confirm those from our post-market surveillance registry that demonstrates a **success rate of 76% in 65 days** in the field for a wide variety of wounds. These wounds range from small, persistent ulcers to large Stage IV ulcers and include dehisced surgical wounds, large venous ulcers, and acute surgical incisions, to name a few. It is important to note that this success rate is on very **difficult wounds that have already been unresponsive to other advanced therapies** such as NPWT and HBO and had been open for an average of 299 days (as a new technology, CDO is typically first tried on challenging, unresponsive wounds). More details of the current registry results can be found on our website (eo2.com).

Additional studies currently in press or in progress: We are conducting a variety of clinical studies, including retrospective analyses and prospective studies. These studies include not only looking at the primary outcome of wound healing, yet also the underlying mechanisms as to how oxygen can affect wound healing. Further information can be found in our white papers on How Oxygen Works in Wound Healing (690024) and How CDO Works (690023). Here is an overview of completed and ongoing studies:

- Dr. Stephanie Wu (Rosalind Franklin University, Chicago, IL): prospective study looking at wound closure, pain reduction (VAS), reduction of inflammatory cytokines, VEGF, genetic markers, quality of life/activity levels, and bioburden reduction. A case study from Dr. Wu's first patient (prior to the study) has been published in Podiatry Today⁴. This case demonstrates a marked **pain reduction** upon application of CDO. See graph from EO₂ Case Study 690036: pain reduced from 8 to 3 upon application, rose to 8 upon withdrawal of CDO during treatment, then reduced quickly to 3 upon reapplication of CDO. Study completed, submitted for publication.
- Dr. Gabriel Urrea-Botero (Gonzaba Medical Group, San Antonio, TX): retrospective analysis on the impact of CDO in chronic toe ulcer healing for 20 patients. As Published in Podiatry Today⁵, results include an overall success rate (full closure) of 74% on wounds that were unresponsive to other therapies, which compares very well to the EO₂ registry (eo2.com). The author highlights a chief benefit being that of high patient compliance (95%), which he attributes to the device's ease of use, the noticeability of improvement within a short period of time, and the reduction of pain. Reprints available (EO₂ White Paper 690076).
- Dr. Mark Couture (Central Texas Veteran's Healthcare Administration, Temple, TX): retrospective analysis of 25 patients in a Veteran's Healthcare Administration environment. As Published in Podiatry Today⁶, results show 68% full closure, both as a stand alone and adjunctive therapy. The author found that CDO improves wound healing potential, even in wounds receiving tissue/skin substitute applications. These outcomes are also compared to outcomes in other published studies, as well as EO₂'s registry. Reprints available (EO₂ White Paper 690080).
- Dr. Larry Lavery (University of Texas Southwestern Medical Center, Dallas, TX): prospective study of 20 patients investigating perfusion changes in the wound bed (using Hyperspectral imaging (Hyper Med), Skin Perfusion Pressure measurements (Vasa med) and Transcutaneous oxygen measurements), changes in inflammatory cytokines (IL-6, IL-8, TNF- α) and growth factors (VEGF, PDGF, IGF, TGF- β), and reduction in bioburden. Enrollment completed.
- Drs. Bijan Najafi, Miguel Montero, Jeffrey Ross, Brian Lepow & Joseph Mills (Baylor College of Medicine, Houston, TX): prospective study of 30 patients investigating effect of CDO on surgical wound closure post minor amputation using a control group (no oxygen). Outcomes being investigated include reduction in post-surgical complications, changes in skin perfusion, changes in quality of life (including pain, anxiety and physiological stress) and assessing user perception of benefit, user-friendliness and acceptability. In progress.
- Dr. Aksone Nouvong (University of California, Los Angeles, CA): prospective trial of 5 patients to assess the oxygen perfusion in patients with chronic venous leg ulcers, and then observing the effect of CDO on perfusion as wound healing progresses. All of the wounds responded positively, with four of five wounds healing completely in 4 weeks, despite having been unresponsive to advanced therapies in other clinical trials. Perfusion changes in the wound bed were noted within one hour of CDO application. Completed, submitted for publication.



References:

1. Lavery LA, Niederauer MQ, Papas KK, Armstrong DG. Does Debridement Improve Clinical Outcomes in People with DFU Ulcers Treated with CDO? Wounds 31(10):246-251 2019. Epub 2019 July 31
2. Niederauer MQ, Michalek JE, Liu Q, Papas, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. J Wound Care 27(9):s30-s45 2018.
3. Bowen J, Ingersoll MS, Carlson R. Effect of CDO on Pain in Treatment of Chronic Wounds. Wound Central 2(4):186-195 2018.
4. Brannick B, Engelthaler M, Jadzak J, Wu S. A Closer Look at Continuous Diffusion of Oxygen Therapy for a Chronic, Painful Venous Leg Ulcer. Podiatry Today 27(11) 2014.
5. Urrea-Botero G. Can Continuous Diffusion of Oxygen Heal Chronic Toe Ulcers? Podiatry Today 28(10) 2015.
6. Couture M. Does Continuous Diffusion Of Oxygen Have Potential In Chronic Diabetic Foot Ulcers? Podiatry Today 28(12) 2015.



December 2019