

EO₂ Clinical Research Summary

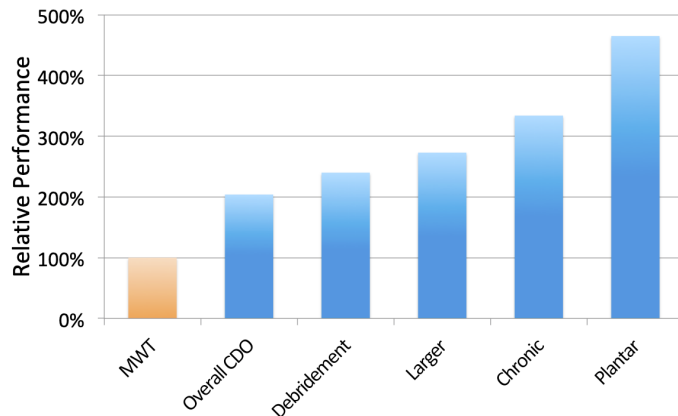
Multicenter DFU Study:^{1,2,3} Results from a Level 1A Diabetic Foot Ulcer clinical trial involving 146 patients across 34 sites show that Continuous Diffusion of Oxygen (CDO) therapy to be statistically significant compared to a placebo arm. The rigor of this study is rare in the medical device world: a fully-blinded, 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 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 increased in size (273%), were more chronic (334%) and were 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.

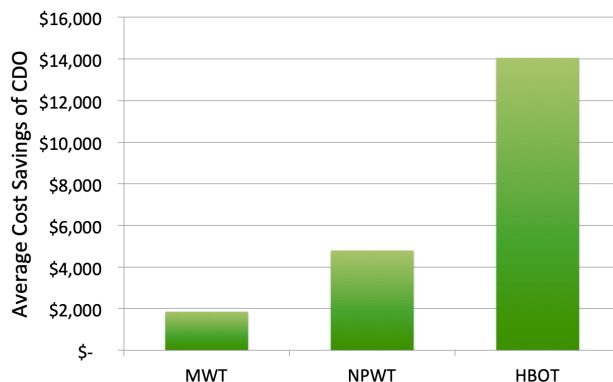
Economic Evaluation Study:⁴ This study used published data to compare the outcomes of CDO therapy versus moist wound therapy (MWT), negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT), with the focus primarily on NPWT as the primary standard of comparison, and report on cost savings and impact on quality life years. The model predicted that continuous diffusion of oxygen would cost \$4,800 less compared to negative pressure wound therapy with a slight increase in quality-adjusted life (extension of life). Lower cost and improved outcomes were observed in most scenario analyses (87% of cost analyses and 90% of quality-adjusted life analyses). The results of this economic evaluation show that CDO therapy should reduce health care economic burden with a modest increase in quality of life outcomes. Authors state that health care decision-makers should consider the inclusion of CDO for the treatment of DFUs.

Pain Study:⁵ Results from a prospective trial of 20 patients to investigate reduction in pain in patients with 23 chronic lower extremity ulcers found that subjects experienced wound associated 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 (100%) experienced complete pain relief regardless of wound closure rate. Multiple subjects reported complete pain relief within hours of application of CDO. Subjects also reported being able to cease using narcotics with CDO.

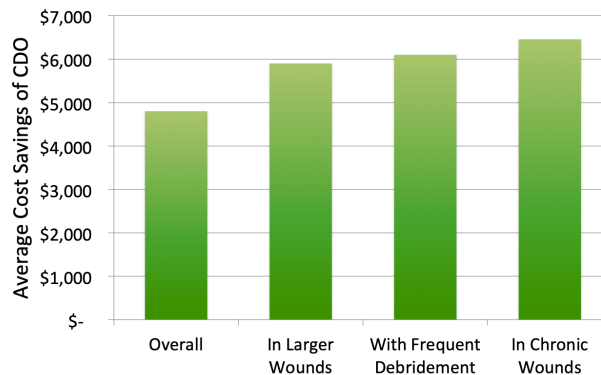
Performance of CDO Relative to MWT



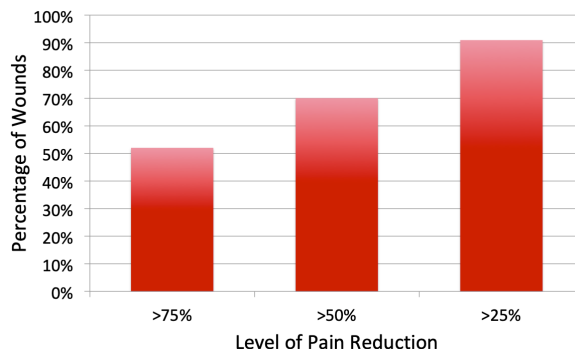
Cost Savings of CDO vs. Other Therapies



Cost Saving of CDO vs. NPWT



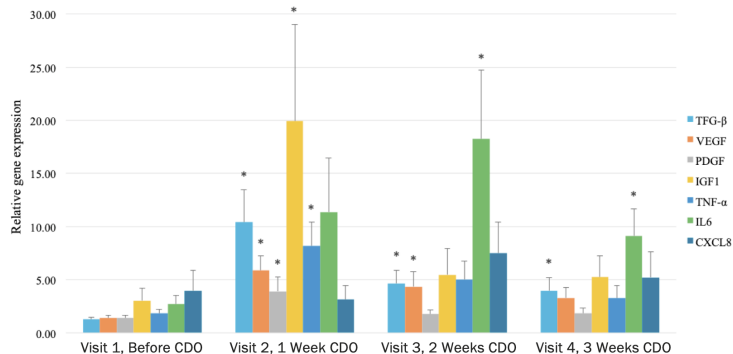
Pain Relief with CDO at First Visit



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Inflammatory Cytokines & Growth Factors, Oxygen Perfusion in Leg Ulcers:⁶

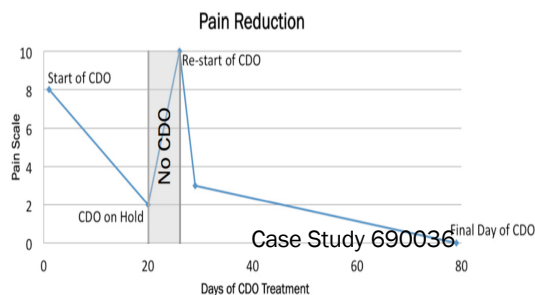
A prospective study of 20 patients investigating inflammatory cytokines (IL-6, IL-8, TNF- α), growth factors (VEGF, PDGF, IGF, TGF- β), perfusion changes peripheral the wound bed, changes in, and reduction in bioburden in a 3 week timeframe. Results showed significant increases in cytokines, growth factors and TCOM one week after application of CDO. Growth factors significantly increased between 280% to 820% in the first week. Several cytokines increased over 400% in the first two weeks and then decreased. Significant increases in TCOM indicate increased oxygen perfusion in wound periphery. Over half the wounds healed at least 50% in 3 weeks.



Wound Healing & Pain Reduction in Toe Ulcers:⁷ A retrospective analysis on the impact of CDO in chronic toe ulcer healing for 20 patients demonstrated an overall success rate (full closure) of 74% on wounds that were unresponsive to other therapies. These results, gathered in an uncontrolled setting, compare 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) on eo2.com.

Use with Skin Substitutes on Leg Ulcers:⁸ A retrospective analysis of 25 patients with chronic wounds in a Veteran's Healthcare Administration environment demonstrated 68% full closure, both as a stand alone and adjunctive therapy. The author found that CDO improves wound healing potential, including those wounds adjunctively 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) on eo2.com.

Pain Reduction in Leg Ulcers:⁹ A case study from Dr. Wu demonstrates a marked pain reduction upon application of CDO. See graph at right from the case study: 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. Reprints available (EO₂ Case Study 690036).



CDO Registry: Published 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:

- **Pain Reduction, Inflammatory Cytokines & Growth Factors, Quality of Life: Leg Ulcers (Rosalind Franklin University)**

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. This pilot study has shown that CDO may facilitate healing of chronic wounds by upregulating growth factors and cytokines needed to facilitate healing and neovascularization while downregulating pro-inflammatory cytokines and tissue-degrading proteases. The proteome analysis data

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correlated well to the histologic analysis of diminished acute and chronic inflammation, neovascularization and new collagen deposition. Study completed, submitted for publication.

- **Oxygen Perfusion & Wound Healing: Chronic Venous Ulcers (UCLA)**

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 80% of 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 and submitted for publication.

- **Reduction in Necrosis, Increase in Skin Perfusion & Quality of Life: Foot Amputations (Baylor College of Medicine)**

Drs. Alejandro Zulbaran, Naima Rodriguez, Brian Lepow, Jeffrey Ross, Bijan Najafi (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. Interim results showed significantly less necrosis with CDO (0% with CDO, 43% in control group) and significantly more complete healing at 4 weeks with CDO (75% with CDO vs 29% control). Average wound length was 70% shorter with CDO. Authors noted a “noticeable trend in favor of CDO to accelerate healing in surgically closed wounds and reduce like hood of AEs”. Study in progress. Interim results published as a poster at the 23rd Congress of the Michael E DeBakey International Surgical Society and available on eo2.com.

- **Reduction in Scarring, Increase in Skin Perfusion: Thyroidectomy¹⁰ (Baylor College of Medicine)**

Drs. Alejandro Zulbaran, Naima Rodriguez, Ram K Mishra, Hector Elizondo, James Suliburk, Bijan Najafi (Baylor College of Medicine, Houston, TX): prospective study of 30 patients investigating effect of CDO on surgical wound closure in patients undergoing thyroidectomy using a control group (no oxygen). Outcomes being investigated include reduction in post-surgical complications, changes in skin perfusion, reduction in scarring and assessing user perception of benefit, user-friendliness and acceptability. Interim results showed significantly less scarring with CDO. Average wound length was 40% shorter with CDO. A comparison of wounds experiencing >10% scar reduction demonstrated significantly better results with CDO: 78% vs. 29% for control group. Authors noted a “better outcomes for scar visualization”. Study in progress. Interim results published as a poster at the 23rd Congress of the Michael E DeBakey International Surgical Society and available on eo2.com.

NOTE: Refer to How CDO Works, LIT 690023, for additional CDO publications and comparison to TO & HBO.

NOTE: A Clinical Research Summary is available for many publications. Available upon request.

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 Niederauer MQ, Michalek JE, Armstrong DG. A prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to sham therapy in the treatment of diabetic foot ulcers. *J Diabetes Science Tech.* 2017, *Special Issue*, 1-9. <https://dx.doi.org/10.1177%2F1932296817695574>

⁴ Chan BCF, Campbell, KE. An economic evaluation examining the cost-effectiveness of continuous diffusion of oxygen therapy for individuals with diabetic foot ulcers. *Int Wound J.* 2020;1-18. <https://doi.org/10.1111/iwj.13468>

⁵ Bowen J, Ingersoll MS, Carlson R. Effect of CDO on Pain in Treatment of Chronic Wounds. *Wound Central* 2(4):186-195 2018.

⁶ Lavery LA, Killeen AL, Farrar D, Akgul Y, Crisologo PA, Malone M, Davis KE. The effect of continuous diffusion of oxygen treatment on cytokines, perfusion, bacterial load, and healing in patients with diabetic foot ulcers. *Int Wound J.* 2020;1-10. <https://doi.org/10.1111/iwj.13490>

⁷ Urrea-Botero G. Can Continuous Diffusion of Oxygen Heal Chronic Toe Ulcers? *Podiatry Today* 28(10) 2015.

⁸ Couture M. Does Continuous Diffusion Of Oxygen Have Potential In Chronic Diabetic Foot Ulcers? *Podiatry Today* 28(12) 2015.

⁹ Brannick B, Engelthaler M, Jazak J, Wu S. A Closer Look at Continuous Diffusion of Oxygen Therapy for a Chronic, Painful Venous Leg Ulcer. *Podiatry Today* 27(11) 2014.

¹⁰ Zulbaran-Rojas et al. CDO Adjunct Therapy to Improve Scar Reduction after Cervicotomy, *JSR* 268;585-94, 2021. <https://doi.org/10.1016/j.jss.2021.07.028>

