

Editorial and Mini-Review: Topical Oxygen Therapy for Diabetic Foot Ulcerations - Avenue Towards New Hope?

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Manuscript submitted December 9, 2019; accepted December 17, 2019; published December 29, 2019

■ Abstract

Diabetic foot complications now represent the 10th leading cause of disease burden and disability. Wound healing is impaired, leading to chronic ulceration. Local high oxygen concentration is required by the metabolically active cells in the wound, which may render the region hypoxic, even in the absence of peripheral arterial disease. Therefore, the contribution of hyperbaric oxygen to improved healing rates has been extensively investigated. More recent developments include products delivering topical oxygen therapy (TOT) directly at the wound site, either by continuous deliv-

ery or by pressurized systems. A very recent systematic review has found that TOT increases wound healing rates in chronic, less severe diabetic foot ulcers (DFUs), and it promotes high rates of healing in more severe ulcers. Thus, TOT appears to be very promising to improve healing in DFUs. We now need more experience regarding its therapeutic place in the algorithm of DFU management and in relation to optimal patient selection.

Keywords: diabetes mellitus • diabetic foot ulcer • vascular disease • topical oxygen therapy • peripheral arterial disease • wound healing

 lower-extremity complications secondary to diabetes now rank as the 10th leading cause of global disease burden and disability [1]. Up to one in 3 of subjects with diabetes are at risk of developing a diabetic foot ulcer (DFU) during their lifetime [2], a condition also associated with an increased risk of lower extremity amputation and mortality [3]. Perhaps the biggest challenge of DFUs is that they are difficult to heal. Indeed, according to the United Kingdom National Diabetic Foot Audit, less than half of all new diabetic foot ulcers are healed by 12 weeks [4]. Even in specialized centers, healing rates for DFUs amount to 22-30% at 20 weeks [5, 6].

Wound healing is a complex pathway involving a dynamic series of interactions between local cells, proteins, proteases, growth factors, and extracellular matrix components [7]. In this process, oxygen is a pivotal factor, because it is critical for

cellular ATP generation, collagen deposition, fibroblast proliferation, angiogenesis, and superoxide production, which allow local tissues to resist infection [8]. Wounds can become increasingly hypoxic as a result of disruption of the vascular flow and/or the increased oxygen demands that accompany the local response to healing [8, 9]. Indeed, the high oxygen demand of metabolically active cells in the wound microenvironment may render the region hypoxic, even in the absence of peripheral arterial disease (PAD) [10].

Therefore, interventions aiming to improve local oxygen delivery hold promise for chronic wound healing. The use of hyperbaric oxygen therapy (HBOT) has received extensive academic interest and widespread clinical adoption. However, the results of several randomized clinical trials (RCTs) have been inconsistent regarding its efficacy in healing DFUs [11, 12]. Furthermore, up to one

third of subjects considered for treatment are unsuitable or intolerant of HBOT because of comorbidities [13]. Of note, HBOT is expensive and not widely available. Hence, products delivering topical oxygen therapy (TOT) either by continuous delivery or pressurized systems have now been developed. These devices deliver oxygen topically, directly into the local injured tissue and can circumvent some of the limitations associated with HBOT. Many of these devices are portable and can even be used at home, which makes them more attractive.

In this volume of *The Review of Diabetic Studies*, Nataraj *et al.* report their findings of a systematic review of TOT on wound healing in DFUs [14]. They included studies of patients with chronic DFUs receiving TOT compared with individuals who received standard care. Overall, 5 studies were reviewed involving 80 participants. The authors concluded that the use of TOT led to a higher complete wound healing rate in chronic, less severe DFUs and also improved the percentage area reduction in more severe ulcers [14].

While the findings by Nataraj *et al.* are encouraging for the use of TOT, we must not ignore several limitations [14]. The first relates to the small sample size. Secondly, most studies had a brief duration of follow-up, mainly between 4-8 weeks, and only 1 study with a 12-week follow-up was included [14]. Moreover, there was significant heterogeneity between the studies in terms of inclusion criteria, duration of ulceration, DFU characteristics, previous foot care, and reporting of results [14]. Furthermore, the authors did not use the 21-point assessment criteria to evaluate the quality of studies [15]. Finally, it was not possible for the authors to conclude on the cost-effectiveness of TOT [14].

Possibly, the most important limitation, and one which may be linked to the definition of chronic DFU used by the authors (i.e. >3 months' duration) is the non-inclusion of further RCTs on TOT. One early randomized study reported no apparent reduction in the cross-sectional area of DFUs; however, it had a sample size of only 28 participants and a 2-week follow-up [16]. Another

larger RCT by Driver *et al.*, including 130 subjects, found no difference in healing rates of DFUs with TOT compared with standard care at 12 weeks [17].

By contrast, 3 studies have yielded positive results [18-20]. Niederauer *et al.* reported an almost two-fold higher rate ($p < 0.033$) of complete DFU closure at 12 weeks in 146 subjects [18]. These authors compared continuously diffused topical oxygen therapy with standard care, including the use of a sham device [18]. The same group also reported similar results with continuously diffused topical oxygen therapy in a smaller study along with the intriguing observation that the efficacy of TOT was greater in more chronic and larger wounds [19]. More recently, Frykberg *et al.* have reported that topical wound oxygen therapy applied with pressure varied cyclically was superior ($p = 0.007$) to sham therapy and standard care in achieving complete wound closure, thereby increasing the likelihood of DFU healing at 12 weeks by up to 4-fold [20].

In conclusion, TOT appears promising in terms of improving healing rates of DFUs [18-20]. Ease of use is a further advantage. Nonetheless, its precise therapeutic role in the algorithm of DFU management requires further elucidation. We also need to know more on both the optimal selection of patients and the window of therapeutic opportunity. Meanwhile, prompt recognition, early specialist referral, and intensive multidisciplinary management of DFUs remain crucial [21].

Disclosures: NP has been an advisory board member of TrigoCare International, Abbott, AstraZeneca, Elpen, MSD, Novartis, Novo Nordisk, Sanofi-Aventis, and Takeda. He has participated in sponsored studies by Eli Lilly, MSD, Novo Nordisk, Novartis, and Sanofi-Aventis, and he received honoraria as a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elpen, Galenica, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Takeda, and Vianex. NP also attended conferences sponsored by TrigoCare International, AstraZeneca, Boehringer Ingelheim, and others. PV has received speaker honoraria from Sanofi Diabetes and MSD.

■ References

1. Lazzarini PA, Pacella RE, Armstrong DG, van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. *Diabet Med* 2018. In press.
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med* 2017. 376(24):2367-2375.
3. Saluja S, Anderson SG, Hambleton I, Shoo H, Livingston M, Jude EB, Lunt M, Dunn G, Heald AH. Foot ulceration and its association with mortality in diabetes mellitus: a meta-analysis. *Diabet Med* 2019. In press.
4. NHS Digital. National diabetes foot care audit 2014-17. Available from: <https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes->

- foot-care-audit.
5. **Game F, Jeffcoate W, Tarnow L, Day F, Fitzsimmons D, Jacobsen J.** The LeucoPatch(R) system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial. *Trials* 2017. 18(1):469.
 6. **Edmonds M, Lazaro-Martinez JL, Alfayate-Garcia JM, Martini J, Petit JM, Rayman G, Lobmann R, Uccioli L, Sauvadet A, Bohbot S, Kerihuel JC, Piaggese A.** Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018. 6(3):186-196.
 7. **Sinno H, Prakash S.** Complements and the wound healing cascade: an updated review. *Plast Surg Int* 2013. 2013:146764.
 8. **Bishop A.** Role of oxygen in wound healing. *J Wound Care* 2008. 17(9):399-402.
 9. **Catrina SB, Zheng X.** Disturbed hypoxic responses as a pathogenic mechanism of diabetic foot ulcers. *Diabetes Metab Res Rev* 2016. 32(S1):179-185.
 10. **Guo S, DiPietro LA.** Factors affecting wound healing. *J Dent Res* 2010. 89(3):219-229.
 11. **Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S.** Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015. (6):CD004123.
 12. **Game FL, Attinger C, Hartemann A, Hinchliffe RJ, Londahl M, Price PE, Jeffcoate WJ, International Working Group on the Diabetic Foot.** IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2016. 32(Suppl 1):75-83.
 13. **Santema KTB, Stoekenbroek RM, Koelemay MJ, Reekers JA, van Dortmont LM, Oomen A, Smeets L, Wever JJ, Legemate DA, Ubbink DT, DAMO2CLES Study Group.** Hyperbaric oxygen therapy in the treatment of ischemic lower extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. *Diabetes Care* 2018. 41(1):112-119.
 14. **Nataraj M, Maiya GA, Gagana K, Hande M, Sunil G, Shenoy R, Prasad SS.** Application of topical oxygen therapy in healing dynamics of diabetic foot ulcers - a systematic review. *Rev Diabet Stud* 2019. 15:74-82.
 15. **Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC, International Working Group on the Diabetic Foot and the European Wound Management Association.** Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol* 2016. 4(9):781-788.
 16. **Leslie CA, Sapico FL, Ginunas VJ, Adkins RH.** Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care* 1988. 11(2):111-115.
 17. **Driver VR, Reyzelman A, Kawalec J, French M.** A prospective, randomized, blinded, controlled trial comparing transdermal continuous oxygen delivery to moist wound therapy for the treatment of diabetic foot ulcers. *Ostomy Wound Manage* 2017. 63(4):12-28.
 18. **Niederauer MQ, Michalek JE, Liu Q, Papas KK, 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* 2018. 27(Sup9):S30-S45.
 19. **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 Sci Technol* 2017. 11(5):883-891.
 20. **Frykberg RG, Franks PJ, Edmonds M, Brantley JN, Teot L, Wild T, Garoufalidis MG, Lee AM, Thompson JA, Reach G, et al.** 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. *Diabetes Care* 2019. In press.
 21. **Vas PR, Edmonds M, Kavarthapu V, Rashid H, Ahluwalia R, Pankhurst C, Papanas N.** The diabetic foot attack: "tis too late to retreat!". *Int J Low Extrem Wounds* 2018. 17(1):7-13.