COMMENT ON LÖNDAHL

Number Eight in the Service of Diabetic Foot Ulcer Healing. Diabetes Care 2020;43:515–517

Robert G. Frykberg, on behalf of the TWO2 Study Group

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We appreciate the thoughtful commentary by Löndahl (1) on our recent article (2) describing the positive results of our double-blinded, randomized, placebo-controlled trial of the effect of cyclical, pressurized Topical Wound Oxygen (TWO2) therapy for healing chronic diabetic foot ulcers (DFUs). Recognizing that no study can be considered perfect in design, execution, or outcomes, we welcome this opportunity to address the concerns raised by Dr. Löndahl pertaining to the aforementioned randomized controlled trial (RCT) (2).

First, we do agree that the results of recent hyperbaric oxygen therapy (HBOT) trials are inconsistent and generally fail to provide robust evidence to support the adjunctive use of HBOT for DFUs (3–5). Much of the failure to provide consistent results is due to study design deficiencies; heterogeneity in study populations, inclusion criteria, and outcome measures (DFU healing vs. amputation); lack of sham controls; and loss of subjects because of adverse events and early terminations (6,7). Furthermore, intention-to-treat (ITT) analyses of all enrolled study populations has not been uniformly reported (3). Another difficulty in this regard is that primary HBOT outcomes obtained at 1-year time points (3,5) are difficult to compare with other DFU therapies that have their primary outcomes assessed at 12 or 20 weeks.

Heterogeneity and discordant results indeed exist in earlier as well as more recent topical oxygen therapy (TOT) RCTs, despite a good body of preclinical and clinical evidence suggesting a beneficial effect on DFU healing (8–10). We concur that as an overall therapy there are differences in outcomes based on the TOT delivery system utilized. TOT devices are clearly not all the same and provide variable delivery of oxygen and pressures topically to wounds.

A specific point of concern raised in the commentary (1) pertained to our group sequential design with specified a priori hard stopping rules after predetermined numbers of patients had completed the 12-week treatment period. The sample size and rationale for this design was clearly explained in the article (2). Importantly, all analyses were done exclusively using the ITT cohorts with no provision for more convenient per-protocol analyses. Upon obtaining a statistically significant treatment effect after the first predetermined 73 patients had completed the active phase of the study (41.7% vs. 13.5%, $P = 0.007$), study enrollment was halted. We would have violated our own protocol had we continued to enroll study subjects for want of "casting a shadow" over the outcomes achieved. We also have to recognize that even with relatively small numbers, a significant magnitude of treatment effect can result in statistical significance. This is best illustrated by the Kaplan-Meier curve in Fig. 2 of the article.

We reject the concern that stratification was necessary, since all adjustments for confounding variables were planned to be handled through multivariate modeling. Randomization yielded three significant baseline differences out of a total of 28 individual or grouped variables, with only CRP levels being higher in the sham control group. Increased ulcer depth (University of Texas [UT] grade) and previous amputation history were more prevalent in the intervention group. While CRP levels and prior amputation history had no effect on outcome, we found that ulcer grade actually strengthened the association between active treatment and wound healing at 12 weeks (odds ratio 6.00 [97.8% CI 1.44, 24.93], $P = 0.004$). We found no center-related associations with outcomes among the well-established diabetic foot study centers.

The point raised concerning the ostensibly low placebo healing rate at 12 weeks (13.5%) and 12 months (27%) is a valid observation and, as the reviewer noted, was similar to the 12-week placebo healing rate (17%) in the recent RCT of Niederauer et al. (10). However, that study only enrolled patients with UT grade 1A ulcers, while our RCT enrolled people with more complex DFUs including up to UT grade 2C. We attribute the placebo healing rate to the randomization only of more difficult-to-heal ulcers. Conspicuously, the HBOT study of Löndahl et al. (3) did not even report 3-month (12-week) healing

Diabetic Foot Education, Phoenix, AZ
Arizona School of Podiatric Medicine, Midwestern University, Glendale, AZ
Corresponding author: Robert G. Frykberg, rgfdpm@diabeticfoot.net

rates. This current TWO2 study (2) is the only such one to also present significant 12-month outcomes, where the placebo healing rate of 27% was indeed similar to the 29% placebo rate reported by Löndahl et al. (3). However, the latter study results, while reported to be based on ITT analysis, were certainly not, since only 54 (57%) randomized patients completed the prescribed study treatments of 40 HBOT sessions. A valid comparison cannot be made when comparing true ITT results with that of per-protocol or other post hoc analyses.

Further wound studies on this underutilized modality would certainly be welcome since it offers a safe, home-based therapy, with proven efficacy when used adjunctively with excellent standards of care.

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