RESPONSE TO COMMENTS ON FEDORKO ET AL.

Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial. Diabetes Care 2016;39:392–399

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We welcome this opportunity to respond to the comments (1–3) regarding our study (4). There are a few common themes that we would like to clarify. The first theme is around the criticism of using "meeting criteria for amputation" instead of "amputation event." It is ideal to use more final patient outcomes in all research; however, the sample size and time needed to recruit and follow patients of sufficient duration to observe final events is often prohibitive. This is the reason why intermediate markers and outcomes are used in many disease areas, including diabetes. In addition, final events like amputations may be an inappropriate outcome in small, randomized controlled trials (RCTs) where other factors may confound the true treatment effect. For example, patient cultural preferences, psychological trauma, and procedure-booking logistics (among other factors) frequently override medical advice about whether and when the limb should be amputated. This (extrinsic to disease) variability precludes using actual amputation event as a consistent outcome measure unless a very large sample and long follow-up times are used. This is impractical and prohibitively costly in placebo-controlled hyperbaric treatment trials. However, Margolis et al. (5) have done it elegantly in a study of different design. This multicenter observational cohort with propensity score matching methodology showed no amputation-sparing effect or improved wound healing in over 700 patients treated with hyperbaric oxygen therapy (HBOT) matched with over 5,000 patients receiving standard wound care. By using the strength of a large sample of patients, this study was able to corroborate the findings we observed in our smaller RCT.

A second criticism theme was around the fact that the "meeting criteria for amputation" outcome was assessed solely on the basis of the digital photography, a method of validation that is not valid or validated (2,3). This criticism is simply incorrect and misleading. As described in the RESEARCH DESIGN AND METHODS section of our article (4), at the primary end point of the study the wound care nurse presented both clinical case information and all patient photographs to the same vascular surgeon who evaluated patients prior to enrollment. The surgeon had a choice (at his discretion) to see the patient in person prior to adjudication. This method of adjudication for indications to amputate has been previously formally validated in direct comparison with personal visits (see refs. 19 and 20 in RESEARCH DESIGN AND METHODS) (4).

Löndahl et al. (1) also questioned the validity of our results because of small differences in patient demographics and shorter follow-up times between our and their (Swedish) study (6). This criticism is unfounded, as one would expect to see some differences in demographics across countries and between populations due to higher rates of diabetes and obesity in North America. Our follow-up time is consistent with several RCTs of other diabetic foot ulcer (DFU) treatment modalities with positive outcomes within 12 weeks (refs. 34–36) (4). There is also very good evidence that the healing rate during the first 4 weeks of treatment is a strong predictor of wound healing (ref. 23) (4). If anything, our results have more relevance to North American populations.

Also, contrary to the assertion by Löndahl et al. (1), transcutaneous oxygen

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pressure measurement ($TcPO_2$) has very poor negative predictive value (7), which limits its clinical/research usefulness.

It is disappointing that Huang (3) asserts "methodological errors" seemingly without carefully reading our article. It is simply unprofessional to criticize an article in a letter to the editor simply because of the preconceived notions of treatment benefit without even reading the methods of an article. First, actual amputations were reported (see RESULTS). Second, off-loading (as required, and as tolerated) was used (see RESEARCH DESIGN AND METHODS). Third, we have clearly stated that Wagner grade 1 wounds "were considered healed" for the purposes of analysis (see RESEARCH DESIGN AND METHODS). Fourth, the primary outcome was assessed at 12 weeks; therefore, the rate of actual amputation after the final adjudication point is irrelevant to the study methodology (see RESEARCH DESIGN AND METHODS).

Contrary to the assertion by Murad (2), there are no known contraindications to HBOT specific to Wagner grade 2 ulcers. We are dismayed at his unprecedented statement that our study was "not patient-centered" and "did not add any new information" because we did not exclude patients with Wagner grade 2 wounds. One should not confuse Undersea and Hyperbaric Medical Society (UHMS) guidelines (8) alignment with U.S. Centers for Medicare & Medicaid Services (CMS) reimbursement policies with scientific evidence. Virtually all RCTs of HBOT to date have included patients with Wagner grade 2 DFU. In this study, we painstakingly assessed a wide range of patient-centered outcomes. We did not see differences in any outcome measures of wound healing rates, quality of life, or independent living between the groups.

Löndahl et al. (1) also refer to the critical issue of an inappropriate placebo used in their double-blind RCT (6), which we discussed in our article, as "irrelevant," a "'bubble' theory" and "of no value." Huang (3) dismisses our concerns (while agreeing at the same time) that the placebo used by Löndahl et al. (6) was not inert. This study (6) is widely quoted and is used in multiple meta-analysis and reviews (including UHMS guidelines) as important level 1 positive evidence for efficacy of HBOT for DFU treatment. Hyperbaric chambers were originally invented to treat "bends" caused by nitrogen bubbles, not to cause them. We stand by our opinion that the placebo used in the study by Löndahl et al. (6) was not a placebo but a nonbenign exposure of control group subjects. "Placebo" patients were subjected to 40 daily 90-min air compressions to 2.5 atmosphere absolute. Such compressed air exposure is beyond the time limits of the generally accepted civilian no-decompression tables (9), putting patients at significant risk of evolving intravascular gaseous nitrogen bubbles. These tables were never tested for repetitive exposures in elderly, sick people with poor peripheral circulation. Therefore, this study regimen may have been associated with observed delayed wound healing and with higher 3-year mortality in the placebo group, as was reported by Löndahl et al. in an abstract form (10). It may also conceivably explain why we were not able to reproduce positive results of the study by Löndahl et al. (6) in our placebo-controlled trial.

Hyperbaric oxygen is a drug delivered in a large pill called a hyperbaric chamber. After several decades of use, it has to be held to the same standards as are applied to other expensive drugs. We were more disappointed than anybody else when we analyzed the data and reviewed it critically in the context of literature. However, as of now, the best available evidence does not provide support for use of HBOT in the patients with chronic diabetic wounds to facilitate healing or prevent the need for amputations.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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