COMMENT 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

Enoch T. Huang

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It was with great interest that I reviewed the article from Fedorko et al. (1), as we had recently completed a comprehensive systematic review of the literature for our clinical practice guideline on the use of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers (2). I looked forward to including a large, randomized, double-blind trial to our analysis, but I was dismayed by the methodological errors I found in the article.

It is obvious that a great deal of work went into the conduct of the trial, and many components to decrease bias should be applauded (e.g., allocation concealment, intention-to-treat analysis, display of Consolidated Standards of Reporting Trials [CONSORT] flow diagram, and use of sham treatments). However, a major flaw in the study lies in its use of photographic adjudication of whether a limb "met the criteria for major amputation" rather than using actual amputation rates as an outcome measure. The fact that there may be patients who "met the criteria for major amputation" but went on to heal undermines the conclusions of this study and introduces both reporting and confirmation bias into the equation. There is no reporting of actual amputation rates anywhere in the article, which raises the question as to why they were not included. Were these subjects lost to follow-up or were the results inconsistent with the goals of the researchers? The only way to alleviate these concerns is to publish the actual amputation rates and validate the decision criteria.

Another issue with the study design is the authors' categorization of a transmetatarsal amputation as a "major" amputation, which is usually defined as an amputation above the ankle. This definition artificially raises the negative outcomes in both groups and grossly mischaracterizes the two outcomes as being equal. Most clinicians would say that the quality of life when preserving a weight-bearing surface is significantly different from one that requires a prosthesis for ambulation. Although all patients underwent "comprehensive wound care," there was no mention of the means of ensuring off-loading of the diabetic foot, which is a prerequisite for healing. The authors incorrectly define a Wagner grade 1 ulcer as a healed wound—it is defined by Wagner (3) as "a superficial ulcer without penetration to deeper layers"—which raises questions about the accuracy of the secondary outcomes of wound healing. A further example of confirmation bias is the willingness of the authors to categorically dismiss the results of two other randomized controlled trials (4,5) for not having inert placebo groups (i.e., 52% O_2), while erroneously stating that their own sham treatment of 26% O_2 was inert.

Publication of negative studies is imperative in the pursuit of the true value of an intervention, and we would be more accepting of a conclusion based on reporting actual amputation rates above the ankle. Inclusion of sham treatment in the control group of hyperbaric oxygen studies is expensive and challenging to implement, but often provides more definitive results. Unfortunately the full potential of this sham-controlled study has not been realized due to its shortcomings.

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References

1. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce

Wound Healing and Hyperbaric Medicine, Adventist Medical Center, Portland, OR

Corresponding author: Enoch T. Huang, enoch.huang@mac.com.

E.T.H. is currently affiliated with Hyperbaric Medicine/Wound Care Clinic, Legacy Emanuel Medical Center, Portland, OR.

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

2. Huang ET, Mansouri J, Murad MH, et al.; UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med 2015;42:205–247

3. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2:64–122

4. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33:998–1003

5. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513–518