RESPONSE TO COMMENTS ON SANTEMA ET AL.

Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower-Extremity Ulcers in Patients With Diabetes: Results of the $DAMO_2CLES$ Multicenter Randomized Clinical Trial. Diabetes Care 2018;41:112–119

Katrien T.B. Santema, Robert M. Stoekenbroek, Mark J.W. Koelemay, and Dirk T. Ubbink, on behalf of the $DAMO_2CLES$ Study Group

Diabetes Care 2018;41:e62–e63 | https://doi.org/10.2337/dci17-0059

We thank Drs. Mutluoglu (1) and Huang (2) for their critical comments. They both express concerns regarding our conclusion based on the results of the $DAMO_2CLES$ [Does Applying More Oxygen (O_2) Cure Lower Extremity Sores?] trial that hyperbaric oxygen therapy (HBOT) does not confer benefit in the treatment of patients with ischemic foot ulcers and diabetes (3).

During the course of the trial, lagging patient inclusion necessitated a downward adjustment of the sample size to meet the time limit imposed by the sponsor of the trial. Nevertheless, this trial still is the largest trial on HBOT in the treatment of ischemic ulcers and allows for future meta-analysis.

Huang (2) was concerned about the variation in clinical practice. The common treatments for diabetic ischemic foot ulcers, such as wound management, vascular surgery, and total contact casting, were allowed in both study arms. Because transcutaneous oximetry measurements during HBOT were not possible in every center, this could not be used as the main selection criterion. Furthermore, more stringent patient selection or stratification would mean statistical analyses between even smaller subgroups, in which significant differences would be very unlikely.

Mutluoglu (1) correctly observed that there was a trend toward improved wound healing and reduced amputation rates, which might have reached statistical significance if we had not been forced to reduce our sample size. This may be a type II error. However, even if a larger sample size might yield any statistically significant difference, it should be weighed against the treatment burden as experienced by a substantial number of patients, the costs, and the availability and proximity of HBOT centers to assess the clinical relevance of HBOT for such patients.

Both commenters pointed to the statistically significant beneficial effects that were observed in patients who completed an HBOT regimen. This result has to be interpreted with caution because a per-protocol analysis is susceptible to bias, as in this trial it included a selected subset of patients who were able to complete the full HBOT regimen.

The imbalance in ulcer severity between the treatment groups occurred randomly and was not statistically significant; 25/60 vs. 33/60 Wagner grade III and IV patients, respectively, equals a risk difference of 13.3% (95% CI −4.4 to 30.0). Again, this may or may not be a type II error, which would be less likely to occur in a larger trial. Besides, even for patients with a Wagner grade II ulcer, poor wound healing and amputation may be a sword of Damocles, which is why we included them for an additional possibility of limb salvage.

We disagree that these limitations render our results "highly questionable" (1) or would suggest HBOT is a "viable adjunctive treatment for enhancing amputation-free survival in the ischemic" diabetic foot ulcer (2). Rather, we believe they provide food for thought, as it remains open for discussion whether our conclusions would have been different or even clinically more relevant if we would have been able to include the initially planned number of patients. Thus, the $DAMO_2CLES$ trial does not close the chapter on the efficacy of HBOT in the treatment of patients with ischemic foot ulcers and diabetes. In particular, the observation of statistically significant benefits among patients who were able to complete an entire HBOT regimen suggests that HBOT may improve outcomes for a subset of patients.

The main message from the $DAMO_2CLES$ trial is that many patients with ischemic ulcers and diabetes are unable to complete a full HBOT regimen, mostly due to their overall bad health condition, and may therefore not benefit from HBOT. The most important aim of future trials should therefore be to identify patients who are likely to derive benefit from HBOT.

Funding. This study received an unrestricted grant from the Netherlands Organisation for Health Research and Development (ZonMw) (project no. 83700.2005).

Department of Surgery, Academic Medical Center, Amsterdam, the Netherlands

Corresponding author: Dirk T. Ubbink, d.ubbink@amc.nl.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.

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

References

1. Mutluoglu M. Comment on Santema et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the $DAMO_2CLES$ multicenter randomized clinical trial. Diabetes Care 2018;41:112–119 (Letter). Diabetes Care 2018;41:e60. https://doi.org/10.2337/dc17-2303

2. Huang E. Comment on Santema et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the $DAMO_2CLES$ multicenter randomized clinical trial. Diabetes Care 2018;41:112–119 (Letter). Diabetes Care 2018;41:e61. https://doi.org/10.2337/dc17-2440

3. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al.; $DAMO_2CLES$ Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the $DAMO_2CLES$ multicenter randomized clinical trial. Diabetes Care 2018;41:112–119